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Archives of Internal Medicine

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THE HEART IN MYXEDEMA

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A review of the literature on the subject of the heart in myxedema reveals a certain amount of confusion concerning the true nature of the cardiac findings. There are those who feel that the findings are purely incidental; others believe that they are inherent in the disease. This lack of unanimity of opinion is found not only in clinical observations but also in experimental, physiologic and pathologic studies. In our attempt to throw light on this problem, it is our purpose to present a critical review of the literature and to report further clinical observations.

REVIEW OF THE LITERATURE

The first extensive study on the heart in myxedema was made by Zondek.[1] His original contribution was based on four cases; later he mentioned additional cases. He found diffuse cardiac enlargement, occasionally limited to the left side, and by fluoroscopy he noted sluggish muscular contractions of the enlarged heart. In the electrocardiographic tracing he observed flat P waves, flat or inverted T waves and low R waves. These changes were interpreted as a result of the diminution in the strength of contractions of the auricle and ventricle inherent in myxedema. Clinically, the symptoms of decompensation were always mild, edema and congestive failure occurring but seldom. The blood pressures were normal. Under thyroid therapy, the condition returned to normal. He suggested using the electrocardiographic findings as an index to the dosage of thyroid to be administered.

From the Thyroid Clinic, the Thorndike Memorial Laboratory, the Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. Zondek, H.: Das Myxödemherz, München. med. Wchnschr. **65**:1180, 1918; **66**:681, 1919; Stoffwechsel und Herzbefunde bei den Kramerschen Myxödemfällen, Berl. klin. Wchnschr. **55**:989, 1918; Behandlung der Herzdilatationen bei Schilddrüseninsuffizienz, Therap. d. Gegenw. **60**:361, 1919; Herz und innere Sekretion, Ztschr. f. klin. Med. **90**:171, 1920; Herzbefunde bei endokrinen Erkankungen, Deutsche med. Wchnschr. **46**:1239, 1920.

Many authors have confirmed Zondek's findings,[2] and Cori [3] reported similar observations in a 4 year old cretin. The eleventh edition of Osler's "Principles and Practice of Medicine" [4] states that in myxedema, "myocardial insufficiency of various grades is not uncommon and may disappear after thyroid treatment is given." Sturgis [5] noted definite cardiac injury in 40 per cent of his cases, and in Lawrence's [6] series, every case of demonstrable myxedema showed signs of cardiovascular disease. Other writers have made additional observations. Gardner [7] noted periods of auricular flutter, arborization block and inverted T waves in the electrocardiogram, which disappeared under thyroid therapy. Lueg [8] questioned whether changes in the electrocardiogram might not be due to changes in the current in passing through the tissues between the heart and the galvanometer, and Tung [9] suggested anoxemia or a myxedematous state of the cardiac muscle as a cause of the changes in the tracing. Holzman [10] felt that possibly the long duration of the myxedema might produce definite organic changes in the heart in some cases. Somewhat similarly, White [11] expressed a belief that coronary disease accounts for the greater frequency of cardiac damage among

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2. (*a*) Fahr, George: Myxedema Heart, J. A. M. A. **84**:345 (Jan. 31), 1925; (*b*) Myxedema Heart, Am. Heart J. **3**:14, 1927. (*c*) Schittenhelm, A., and Eisler, B.: Ueber die Wirksamkeit des Thyroxins bei endokrin bedingten Störungen, Klin. Wchnschr. **6**:1935, 1927. (*d*) Amargos, A.: Clinical Aspects of Myxedematous Cardiac Insufficiency, An. Fac. de med., Montevideo **13**:339, 1928. (*e*) Blumer, George, in Bedside Diagnosis, by American authors, Philadelphia, W. B. Saunders Company, 1928, vol 3. (*f*) Duden, C.: Myxedema with Cardiac Decompensation and Hypertension Which Disappeared with Thyroid Medication, J. Missouri M. A. **26**:25, 1929. (*g*) Davis, J. C.: Myxedema Heart with Report of One Case, Ann. Int. Med. **4**:7, 1931. (*h*) Norris, G. W., and Landis, H. R. M.: Diseases of the Chest, ed. 4, Philadelphia, W. B. Saunders Company, 1929.

3. Cori, G.: Experimentelle Untersuchungen an einem kongenitalen Myxödem, Ztschr. f. d. ges. exper. Med. **25**:150, 1921.

4. Osler, William: Principles and Practice of Medicine, ed. 11, New York, D. Appleton and Company, 1930.

5. Sturgis, C. C.: The Cardiovascular System in Diseases of the Thyroid Gland, J. Michigan M. Soc. **26**:1, 1927.

6. Lawrence, C. H.: The Physiological Background for the Symptoms of Thyroid Failure, Boston M. & S. J. **196**:2, 1927.

7. Gardner, E. L.: Hypothyroidism with Special Reference to the Minor Deficiencies, Journal-Lancet **44**:10, 1924.

8. Lueg. W.: Ueber das Electrokardiogramm des Myxödems, Ztschr. f. klin. Med. **104**:337, 1926.

9. Tung, C. L.: The Status of the Heart in Myxedema, Am. Heart J. **6**:734, 1931.

10. Holzman, J. E.: Myxedema Heart, Am. Heart J. **4**:351, 1929.

11. White, P. D.: Heart Disease, New York, The Macmillan Company, 1931.

the older cases of myxedema. Ayman, Rosenblum and Falcon-Lesses [12] suggested that enlargement of the heart, with its return to normal following thyroid treatment, is the one diagnostic feature of the heart in myxedema, since the other abnormalities are usually found in all cases of myxedema.

Several writers have limited their reports to electrocardiographic findings. A number of them [13] have corroborated Zondek's original findings. Others [14] reported similar observations both in cretins and in patients with myxedema. In two cases Chini [15] found the typical coronary T wave described by Pardee.[16] Hamburger, Lev, Priest and Howard [17] found that the electrocardiographic changes may precede the change in the basal metabolic rate. Lesser and Anderson [18] described a patient, aged 51, with myxedema who had attacks of paroxysmal tachycardia of seventeen years' duration. Two electrocardiograms taken before treatment was instituted showed, in the first instance, paroxysmal nodal tachycardia, with a pulse rate of 168 and depressed S T intervals, and, in the second instance, a sinus bradycardia with a rate of 40, inversion of the T waves in all leads and a low take-off of S T, with upward convexity in lead II. Six months after treatment the electrogardiogram showed normal sinus rhythm, a rate of 79, T upright in all leads and a normal S T interval.

12. Ayman, D.; Rosenblum, H., and Falcon-Lesses, M.: Myxedema Heart Without Evidence of Cardiac Insufficiency: Report of Two Cases, J. A. M. A. **98**: 1721 (May 14) 1932.

13. (*a*) Means, J. H., and Richardson, E. P.: Diseases of the Thyroid, in Christian, H. A.: Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1929, vol. 4. (*b*) Willius, F. A., and Haines, S. F.: Status of the Heart in Myxedema, Am. Heart J. **1**:67, 1925. (*c*) Reid, W. D., and Kenway, F. V.: Electrocardiographic Signs Associated with Low Basal Metabolism, Endocrinology **13**:191, 1929. (*d*) White, P. D., and Aub, J. C.: The Electrocardiogram in Thyroid Disease, Arch. Int. Med. **22**:766 (Dec.) 1918.

14. Thacher, C.: The Electrocardiogram in Cretinism and Mongolian Idiocy, Am. J. Dis. Child. **28**:25 (July) 1924. Nobel, E.; Rosenblüth, A., and Samet, B.: Das Electrokardiogramm des kindlichen Myxödems, Ztschr. f. d. ges. exper. Med. **43**:332, 1924. Thacher, C., and White, P.: The Electrocardiogram in Myxedema, Am. J. M. Sc. **171**:61, 1926.

15. Chini, V.: Breva nota di cardiologia sul mixedema, Cuore e circolaz. **13**: 32, 1929.

16. Pardee, H. E. B.: Heart Disease and Abnormal Electrocardiograms, Am. J. M. Sc. **169**:270, 1925.

17. Hamburger, W. W.; Lev, M. W., Priest, W. S., and Howard, H. C.: The Heart in Thyroid Disease, Arch. Int. Med. **43**:1 (Jan.) 1929.

18. Lesser, H., and Anderson, E. M.: Three Cases of Adult Myxedema in Women, Endocrinology **15**:5, 1931.

Others have paid attention only to changes in the size of the heart. Several authors [19] reported findings similar to those of Zondek. Christian [20] in his early cases did not note these changes, but later [21] mentioned that in a few patients with myxedema who showed enlargement of the heart and symptoms of congestive failure, digitalis medication was without effect, while thyroid therapy resulted in marked improvement. Wegelin [22] expressed the opinion that enlargement of the heart is due less to changes in the myocardium than to a decrease in the number of red blood cells and to bradycardia. Eppinger [23] described many cases resembling myxedema in their appearance (no basal metabolic rates are recorded), with enlargement of the heart and symptoms of heart failure, that showed a complete return to normal following thyroid treatment.

In contrast to the workers mentioned, there are those who feel that changes in the heart in myxedema are of no great importance or significance. Cabot,[24] Cecil,[25] Vaquez [26] and MacKenzie [27] made no mention of the status of the heart in myxedema. Hirschfelder [28] stated that cardiac symptoms of cachexia thyreopriva are not prominent features of the disease. Means and Richardson [13a] noted that the lack of tone to the extent of gross cardiac enlargement occurs but rarely, and Means, White and Krantz [29] stated that about all that can be said is that occa-

19. Assmann, H.: Das Myxödemherz, München. med. Wchnschr. **66**:9, 1919. Meissner, R.: Zur Klinik des Myxödemherzens, München. med. Wchnschr. **67**: 1316, 1920. Zandrén, S.: Zur Frage des Myxödemherzens, Zentralbl. f. Herz. u. Gefässkr. **14**:183, 1922. Zins, B., and Rösler, H.: Kasuistischer Beitrag zur Beeinflussung des Myxödemherzens durch Thyreodin, Wien. klin. Wchnschr. **39**: 1360, 1926.

20. Christian, H. A.: The Heart and Its Management in Myxedema, Rhode Island M. J. **8**:109, 1925.

21. Christian, H. A.: Myocardial Disturbances Due to Abnormal Thyroid Function and Their Management, Pennsylvania M. J. **32**:70, 1928.

22. Wegelin, C.: Drüsen mit innerer Sekretion, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 353.

23. Eppinger, H.: Zur Pathologie und Therapie des menschlichen Ödems, Berlin, Julius Springer, 1917.

24. Cabot, Richard C.: Physical Diagnosis, ed. 10, New York, William Wood & Company, 1930.

25. Cecil, R. L.: Text Book of Medicine, ed. 3, Philadelphia, W. B. Saunders Company, 1930.

26. Vaquez, H.: Diseases of the Heart, Philadelphia, W. B. Saunders Company, 1924.

27. MacKenzie, J.: Diseases of the Heart, ed. 5, New York, Oxford University Press, 1925.

28. Hirschfelder: Diseases of the Heart and Aorta, ed. 3, Philadelphia, J. B. Lippincott Company, 1918, p. 675.

29. Means, J. H.; White, P. D., and Krantz, C. I.: Observations on the Heart in Myxedema, Boston M. & S. J. **195**:10, 1926.

sionally a patient with myxedema presents a type of cardiac flabbiness which in reality is due to the low level of the metabolic ratio. In a series of fifty-eight cases, Case [30] did not associate the few cardiac findings with myxedema. Curschmann [31] noted the changes in the size of the heart, but he found no variation in the electrocardiogram, while Doxiades and Pototzky [32] observed electrocardiographic changes without cardiac enlargement. Coelho [33] does not consider the electrocardiographic findings typical of myxedema, as he has seen similar tracings in other diseases, notably, in Addison's disease and in Fröhlich's syndrome. He does not believe that cutaneous resistance plays any part in the picture, since in these cases the use of needle electrodes gave the same results as the use of ordinary electrodes.

In addition to the work on the size of the heart and electrocardiographic changes in myxedema, numerous isolated observations on other changes of the cardiovascular system associated with thyroid deficiency have been reported. Most important among these observations have been those on heart block, angina pectoris, edema and hypertension.

Incomplete heart block was present in a case reported by Luten.[34] The patient improved under thyroid therapy, while in a case of complete heart block reported by Aub and Stern [35] thyroid therapy had no appreciable effect. A few observations have been made on the effect of thyroid therapy on complete heart block in which evidence of myxedema was lacking. Blackford and Willius [36] expressed the belief that thyroid medication quickens the idioventricular rate, the auricular rate increasing much earlier than the ventricular. In a case reported by Drake [37] the final picture was that of normal rhythm and intraventricular

30. Case, C. E.: An Analysis of Fifty-Eight Cases of Myxedema, Clifton M. Bull. **11**:112, 1925.

31. Curschmann, H.: Ueber Myxödem der Erwachsenen, Med. Klin. **22**:559, 1926.

32. Doxiades, L., and Pototzky, C.: Die Bedeutung der kardiovasculären Untersuchungsmethoden für die Beurteilung des Mongolismus und des Myxödems beim Kinde, Klin. Wchnschr. **6**:1326, 1927.

33. Coelho, E.: Les troubles cardiaques dans la maladie de Basedow et le myxoedème, Ann. de méd. **30**:3, 1931.

34. Luten, D.: Myxedema with Partial Heart Block and Severe Anemia Both of Which Disappeared Under Thyroid Therapy, J. Missouri M. A. **26**:73, 1920.

35. Aub, J. C., and Stern, N. S.: The Influence of Large Doses of Thyroid Extract on the Total Metabolism and Heart in a Case of Heart Block, Arch. Int. Med. **21**:130 (Jan.) 1918.

36. Blackford, J. M., and Willius, F. A.: Chronic Heart Block, Am. J. M. Sc. **154**:585, 1917

37. Drake, E. H.: A Case of Complete Heart Block with Interesting Reaction to Drugs, Am. Heart J. **31**:560, 1928.

block. Willius [38] reported two cases of myxedematous bradycardia, one showing a complete heart block and the other a sinus bradycardia, both with the Adams-Stokes syndrome. The patients were treated with thyroxin, U. S. P., and in each case the symptoms of the syndrome disappeared.

The possibility of a direct association between cardiac pain and myxedema was suggested in a communication by Hertoghe [39] in 1914. He thought that pain was due to myxedematous infiltration of the nerve cells of the supporting connective tissue. He also considered the possibility of cardiac pain resulting from too vigorous treatment with thyroid. Sturgis and Whiting [40] and Sturgis [41] suggested that arteriosclerosis is a factor in the causation of angina pectoris, but he expressed the belief that anemia is of extreme importance because of the resulting added strain on the heart. Means, White and Krantz,[29] on the other hand, thought that anemia is not an important factor since there is not much acceleration of the blood flow in anemia. In their opinion, the attacks of angina pectoris may be the result of thyroid therapy, particularly in the cases associated with arteriosclerosis. Abrami, Brule and Heitz [42] agreed with this theory. In contrast, Laubry, Mussio-Fournier and Walser [43] were of the opinion that the arteriosclerosis plays a possible part in the production of angina pectoris, but they thought that the angina is functional in origin since it responds so well to treatment. They also discussed the possibility of its being related to hypotonicity of the myocardium. Likewise, Ziskin [44] reported a case of myxedema heart associated with angina pectoris in which disappearance of the latter symptoms followed treatment. Finally, Blumgart, Gargill and Gilligan [45] suggested that the pain results from an increased flow of the blood following thyroid therapy, especially in cases in which there is arteriosclerotic narrowing of the coronary vessels.

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38. Willius, F. A.: Thyroid Preparations in the Treatment of the Stokes-Adams Syndrome, Canad. M. A. J. **14**:1072, 1924.

39. Hertoghe, E.: Thyroid Deficiency, M. Rec. **86**:489, 1914.

40. Sturgis, C. C., and Whiting, W. B.: The Treatment and Prognosis in Myxedema, J. A. M. A. **85**:2013 (Dec. 26) 1925.

41. Sturgis, C. C.: Angina Pectoris as a Complication in Myxedema and Exophthalmic Goitre, Boston M. & S. J. **195**:351, 1926.

42. Abrami, P.; Brule, M., and Heitz, J.: Deux cas d'angine de poitrine avec myxoedème. Aggravation de l'hypertension par l'opothérapie, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:712, 1925.

43. Laubry, C., Mussio-Fournier, and Walser, J.: Syndrome angineux et insuffisance thyroïdienne, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:1592, 1924.

44. Ziskin, T.: Angina Pectoris Associated with Myxedema Heart, U. S. Vet. Bur. M. Bull. **6**:24, 1930.

45. Blumgart, H. L.; Gargill, S. L., and Gilligan, D. C.: Studies on the Velocity of Blood Flow, J. Clin. Investigation **9**:1, 1930.

There is little mention in the literature concerning the relationship between myxedema and hypertension. Means and Richardson [13a] stated that hypertension may exist with, but is not a part of, myxedema. Abrami, Brule and Heitz [42] reported two cases in which the hypertension was increased as a result of thyroid treatment, and Duden [2f] reported a case of myxedema in which an elevated blood pressure returned to normal following treatment.

The relation of thyroid therapy to edema in cases of myxedema has received some attention. Wenckebach [46] stated that in myxedema there is retention of water as a consequence of the insufficient thyroid secretion and that the water is expelled by thyroid treatment. March [47] expressed the belief that in his cases no disease of the heart or kidney was present, but that the ascites and peripheral edema, which cleared up with thyroid medication, were the result of the myxedema itself. Sainton, Doumer and Véran [48] stated that certain cases of cardiorenal disease are merely cases of hypothyroidism with edema, associated with renal failure, which respond very well to thyroid treatment.

Mention was made in the opening paragraph that the lack of unanimity of opinion as to this problem included not only clinical but pathologic and physiologic studies as well. Ord,[49] in 1880, described the pathologic findings in a case of myxedema. The heart was hypertrophied, flabby and dilated, and on section the heart muscle showed the connective tissue swollen and abundant and a great excess of mucin yielding interstitial cement. Similar changes were reported in the transactions of the clinical society of London in 1888 [50] and by deBarry in 1899.[51] In a case reported by Fishberg,[52] the myocardium exhibited small scars and atheromatous changes in the large blood vessels and in the coronary arteries. Schultz [53] found a peculiar edematous swelling of the aortic leaflets, marked changes in the nuclei and granular degenera-

46. Wenckebach, K.: Heart and Circulation in a Tropical Avitaminosis (Beri-Beri), Lancet **2**:265, 1928.

47. March, H. E.: Myxedematous Ascites Removed by Thyroid Extract, Am. J. M. Sc. **172**:585, 1926.

48. Sainton, P.; Doumer, E., and Véran, P.: Syndrome cardio-rénal et hypothyroïdie, Ann. de méd. **24**:513, 1928.

49. Ord, W. M.: Cases of Myxedema, Tr. Clin. Soc. London **13**:15, 1880.

50. Report of a Committee of the Clinical Society of London, Tr. Clin. Soc. London, 1888, supp. vol. 21.

51. deBarry, J.: Rachitischer Zwergwuchs, Endocarditis chronica, das Bild infantilen Myxödems vortäuschend, Arch. f. Kinderh. **26**:253, 1899.

52. Fishberg, A. M.: Arteriosclerosis in Thyroid Deficiency, J. A. M. A. **82**: 463 (Feb. 9) 1924.

53. Schultz, A.: Ueber einen Fall von Athyreosis congenita (Myxödem) mit besonderer Berücksichtigung der dabei beobachteten Muskelveränderungen, Virchows Arch. f. path. Anat. **232**:302, 1921.

tion of the heart fibers. He did not find mucoid degeneration, but he was sure of the presence of edema between the fibers. Eppinger [23] spoke of fragile and brittle hearts with small scattered scars of the myocardium. Scholz [54] considered the pathologic changes in the heart in myxedema as merely incidental.

Tatum,[55] Benson,[56] Pick and Pinelas,[57] Horsley [58] and Goldberg,[59] working on thyroidectomized animals (rabbits, dogs, cats, sheep and goats), noted in some instances degeneration of the individual muscle fibers of the myocardium and edema of the interfibrillar tissues; in others, dilated hearts with a pale, flabby myocardium, and in others, evidence of pathologic changes in the pericardial sac. Goldberg [59] concluded that "the number of animals and the constant results obtained, also the fact that similar changes are observed in human cretins, make it almost certain that the organ changes found in these animals are the results of thyroidectomy." On the contrary, Kishi [60] and Brooks, Harlow and Larkin [61] concluded from their postmortem studies on animals that the cardiac signs and symptoms produced as a result of hypothyroidism were not due to alterations in the heart muscle.

In the field of experimental physiology, interest has centered chiefly on a study of the electrocardiographic changes in thyroidectomized animals. After total thyroidectomy on dogs, Coelho [33] noted changes in the electrocardiogram similar to those reported by Zondek. Burlage [62] made similar observations on his experimental cretin lambs. In contrast, Lueg,[8] who used thyroidectomized dogs, lambs, goats and rabbits, failed to find changes in the electrocardiogram such as are found in myxedema in man.

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54. Scholz, W., Myxödem, in Kraus, F., and Brugsch, T.: Spezielle Pathologie und Therapie inneren Krankheiten, Berlin, Urban & Schwarzenberg, 1919.

55. Tatum, A. L.: Morphological Studies in Experimental Cretinism, J. Exper. Med. **17**:636, 1913.

56. Benson, W.: Beitrag zur Kenntnis der Organveränderungen nach Schilddrüsen Extirpation bei Kaninchen, Virchows Arch. f. path. Anat. **170**:229, 1902.

57. Pick, E., and Pinelas, F.: Untersuchungen über die physiologisch wirksame Substanz der Schilddrüse, Ztschr. f. exper. Path. u. Therap. **7**:518, 1909.

58. Horsley, V.: The Thyroid Gland: Its Relation to the Pathology of Myxedema and Cretinism, Brit. M. J. **1**:211, 1885.

59. Goldberg, S.: Changes in Organs of Thyroidectomized Sheep and Goats, Quart. J. Exper. Physiol. **17**:15, 1927.

60. Kishi, K.: Beiträge zur Physiologie der Schilddrüse, Virchows Arch. f. path. Anat. **176**:260, 1904.

61. Brooks, Harlow, and Larkin, J.: A Brief Experimental Study of the Morphology of the Heart Muscle Following Hypothyroidism, Am. J. M. Sc. **155**: 66, 1918.

62. Burlage, S. R.: The Characteristic Electrocardiogram of the Cretin Sheep, Proc. Soc. Exper. Biol. & Med. **19**:425, 1922.

CLINICAL OBSERVATIONS

Our observations are based on a study of thirty-five cases of myxedema seen in the clinic for patients with diseases of the thyroid gland at the Boston City Hospital during the past seven years. The method of study was as follows:

After the diagnosis of myxedema was definitely established both clinically and by basal metabolic tests, roentgen plates were taken of the heart at a distance of 7 feet, and electrocardiograms were made. In the latter we noted the rhythm, rate, time of conduction, direction and amplitudes of the complexes. Treatment was then begun, and in a majority of cases thyroid tablets made from the fresh glandular material were prescribed. Whenever possible, basal metabolic tests, roentgen examinations and electrocardiograms were made at frequent intervals. The blood pressure readings were also noted. Fluoroscopic studies were made as often as possible.

In view of the fact that we were dealing largely with outpatients, it was not always possible to secure proper cooperation. Several patients did not return for treatment after the diagnostic studies were made, and others did not return for proper follow-up studies after treatment was instituted.

The results of our studies are given in tables 1, 2 and 3. For the sake of brevity, we have included in these tables only those cases showing changes in the electrocardiogram. Cases 30, 31 and 33 are not included in the statistical survey, for reasons to be mentioned later.

Summary of Findings in Tables.—The basal metabolic rates ranged from —12 to —59, with an average rate of —33. The P waves were low in all but one case. The T waves were low, flat or inverted, in every case returning to the normal deflection after the administration of thyroid (fig. 1). Increased P R intervals were present in four of the cases. In three, the conduction time returned to normal following treatment (fig. 2), whereas in the fourth there was an increase in time. The amplitudes of the R waves ranged from 3 to 8 mm., with an increase in height in each case following therapy. Three cases presented convex S T intervals, which returned to normal after treatment (fig. 3). One patient (case 6) discontinued her treatment, and the electrocardiogram showed a complete return to the abnormal type. With resumption of the thyroid therapy, the normal tracing was again seen. In seven cases there was enlargement of the heart, particularly to the left. As a result of the treatment, three cases showed a return to normal, two a diminution in size and one, no change at all. Two of the patients were subjected to fluoroscopic examination; they showed, in addition to the dilatation, markedly diminished pulsations of the heart. There was not much change in size, but a definite increase of the cardiac excursions was noted very soon after treatment was instituted. In patient 34 there developed, while in the hospital, a hydropneumothorax with no apparent

TABLE 1.—*Findings in Thirteen Cases of Myxedema*

Case	Sex	Age	Basal Metabolic Rate	Comment	Electrocardiogram							Blood Pressure	
					Rhythm Rate *	P Waves	T_1	T_2	T_3	Axis Ampl.	Comment	Roentgenogram	Systolic	Diastolic
4	F	35	−37	Before treatment	N.S.R. 73	Norm.	Inverted	Norm.	Norm.	LVP 5	.....	Normal, Tr.d., 12.8		
28	F	42	−43	Before treatment	N.S.R. 100	Flat	Inverted	Flat	Flat	Norm. 5	.....	Enlarged, Tr.d., 15.6	122	86
10	F	54	−22	6 yrs. after treatment began	N.S.R. 91	Low	Flat	Flat	Flat	Norm. 5	.....	Normal	160	90
			−22	9 mos. later	N.S.R. 73	Low	Flat	Flat	Flat	LVP 6	.....	.....	140	80
			+ 4	7 wks. after last treatment	N.S.R. 83	Norm.	Norm.	Norm.	Inverted	LVP 13				
17	F	40	−20	1 yr. after treatment began	N.S.R. 70	Low	Inverted	Inverted	Inverted	LVP 6	Convex S T	Normal	90	70
			− 8	3 yrs. after last treatment	N.S.R. 83	Norm.	Norm.	Norm.	Flat	Norm. 10	Norm. S T	.....	122	70
6	F	42	−43	Before treatment	N.S.R. 90	Low	Flat	Flat	Inverted	Norm. 3	.....	Enlarged, Tr.d., 14.3	112	68
				4 days after treatment	N.S.R. 95	Norm.	Norm.	Norm.	Inverted	Norm. 5				
			−34	15 days after treatment	S.A.T. 133	Norm.	Norm.	Norm.	Inverted	Norm. 7	.....	.....	102	60
			+17	27 days after treatment	S.A.T. 120	Norm.	Norm.	Norm.	Norm.	Norm. 10	.....	Normal, Tr.d., 11		
			−34	No treatment for 2 mos.	N.S.R. 88	Low	Flat	Inverted	Inverted	Norm. 6	.....	Normal		
				1 mo. after treatment began	S.A. 80	Norm.	Norm.	Norm.	Inverted	Norm. 7				
20	F	27	−59	Before treatment	N.S.R. 79	Low	Flat	Low	Low	Norm. 7	P R 0.24	Enlarged, Tr.d., 15	100	70
			−14	9 mos. after treatment	N.S.R. 71	Norm.	Norm.	Norm.	Norm.	Norm. 11	P R 0.16	Normal, Tr.d., 13.8	124	70
26	M	62	−26	Before treatment	N.S.R. 79	Low	Low	Low	Flat	Norm. 6	P R 0.24	Normal, Tr.d., 13.9	158	104
			− 2	2½ mos. after treatment	N.S.R. 79	Norm.	Norm.	Norm.	Norm.	Norm. 10	P R 0.28			
29	F	58	−35	Before treatment	N.S.R. 63	Low	Inverted	Inverted	Inverted	LVP 5	Convex S T	Enlarged, Tr.d., 16.3	104	62
			−20	6 days after treatment	N.S.R. 71	Norm.	Norm.	Norm.	Flat	LVP 5	Norm. S T			
			+ 4	15 days after treatment	N.S.R. 79	Norm.	Norm.	Norm.	Norm.	LVP 10	.....	Normal, Tr.d., 12.2	112	66
32	M	60	−35	Before treatment	S.B. 49	Low	Flat	Flat	Flat	Norm. 8	High resistance	Enlarged, Tr.d., 17.8	104	70
			+ 5	3 wks. after treatment	N.S.R. 75	Norm.	Norm.	Norm.	Norm.	Norm. 9		Enlarged, Tr.d., 17.6	108	62
34	F	72	....	Before treatment	....	.....	.....	.....	.....	.....	.....	Enlarged to left	110	70
				(4/23/32)	....	.....	.....	.....	.....	.....	.....	Sclerotic arch		
				4/27/32	S.A. 52	Low	Flat	Flat	Flat	Norm. 4.5	P R 0.26			
			−12	5/ 4/32										
				5/10/32	....	.....	.....	.....	.....	.....	.....	Fluoroscopy †		
			−10	Started on treatment										
				5/16/32	N.S.R. 64	Low	Low	Inverted	Inverted	LVP 6	P R 0.28			
				5/17/32	..... .	.....	.....	.....	.....	.....	.....	Fluoroscopy †		

			− 6	5/21/32	N.S.R.	65	Low	Diphasic	Diphasic	Flat	LVP	6	P R 0.24			
				5/25/32	.....		.....	.....	.....	.....	.....		.....	Enlarged, Tr.d., 14.6 Fluoroscopy †		
			+ 5	5/28/32	S.A.	80	Norm.	Diphasic	Low	Flat	LVP	7	P R 0.24			
				6/ 2/32	.....		.....	.....	.....	.....	.....		.....	Normal, Tr.d., 12.7 Fluoroscopy †		
				6/ 5/32	S.A.	80	Norm.	Low	Norm.	Flat	LVP	7	P R 0.22			
			+ 8	6/10/32	N.S.R.	100	Norm.	Norm.	Norm.	Flat	LVP	5.5	P R 0.22	.....	120	64
				6/13/32	.....		.....	.....	.....	.....	.....		.....	Normal, Tr.d., 13.4		
				6/20/32	N.S.R.	95	Norm.	Low	Norm.	Norm.	LVP	7	P R 0.20			
				6/22/32	.....		.....	.....	.....	.....	.....		.....	Normal, Tr.d., 13		
17	F	37	−31	Before treatment	S.A.	85	Low	Flat	Inverted	Inverted	Norm.	8	Convex S T	None	140	90
			−18	3 mos. after treatment	S.A.T.	110	Low	Flat	Flat	Flat	Norm.	6	Norm. S T	.....	118	84
				5 mos. after treatment	S.A.T.	111	Norm.	Norm.	Norm.	Flat	Norm.	10	.....	Normal, Tr.d., 15.4		
			+ 7	8 mos. after treatment	S.A.	88	Norm.	Norm.	Norm.	Inverted	Norm.	9				
55	F	50	....	Before treatment (5/ 5/32)	N.S.R.	60	Low	Flat	Inverted	Inverted	Norm.	4	.....	Enlarged, Tr.d., 20 (40 inch distance)	120	72
				5/10/32	.....		.....	.....	.....	.....	.....		.....	Fluoroscopy ‡		
			−30	Started on treatment 5/18/32	.....		.....	.....	.....	.....	.....		.....	Enlarged, Tr.d., 19.9		
			−26	5/23/32	N.S.R.	58	Low	Flat	Flat	Diphasic	LVP	5		(40 inch distance)		
				5/25/32	.....		.....	.....	.....	.....	.....		.....	(7 ft.) Tr.d., 17.7		
			−20	5/28/32	N.S.R.	60	Low	Flat	Flat	Inverted	Norm.	4.5	.....	Fluoroscopy ‡		
				6/ 2/32	.....		.....	.....	.....	.....	.....		.....	Enlarged, Tr.d., 17.8 Fluoroscopy ‡		
				6/ 5/32	S.A.	67	Norm.	Low	Flat	Inverted	Norm.	5	.....	.....	90	60
			−18	6/10/32	N.S.R.	68	Norm.	Norm.	Low	Inverted	LVP	6	.....	.....	118	65
				6/14/32	.....		.....	.....	.....	.....	.....		.....	Enlarged, Tr.d., 16.2		
			−11	6/23/32	N.S.R.	60	Norm.	Norm.	Flat	Inverted	LVP	8				
30	F	60	−31	Before treatment	N.S.R.	60	Norm.	Inverted	Inverted	Norm.	LVP	12	Convex S T	Normal, Tr.d., 14	180	120
			+11	Months after treatment	N.S.R.	79	Norm.	Inverted	Inverted	Norm.	LVP	18	Convex S T	Enlarged, Tr.d., 17.6	108	62

* N.S.R. = normal sinus rhythm. S.A. = sinus arrhythmia. S.A.T. = sino-auricular tachycardia. S.B. = sinus bradycardia. Norm. = normal amplitude and direction of waves. LVP = left ventricular predominance. Ampl. = amplitude of R wave in its highest lead. Tr.d. = transverse distance.

† 5/10/32: Small hydropneumothorax on right side of heart, transversely enlarged. Pulsation of heart markedly diminished in intensity and excursion.
5/17/32: Fluid still present. Heart enlarged to left. Pulsations definitely increased over those of previous record but still below normal.
5/25/32: Small amount of fluid at left base. Heart slightly enlarged. Pulsations still further increased in intensity.
6/ 2/32: Fluid gone. Heart slightly enlarged to left. Pulsations normal in intensity and excursion.

‡ 5/10/32: Excursion of diaphragms limited. Supracardiac area increased. Heart enlarged transversely. Pulsations markedly diminished; at times imperceptible.
5/28/32: Heart enlarged transversely. Pulsations markedly increased over those on previous examination, but still below normal limits.
6/ 2/32: Heart still enlarged transversely. Pulsations of heart now within normal limits.

cause. This condition cleared up entirely when the patient received thyroid medication. Before treatment, the systolic blood pressure ranged from 90 to 160 with an average of 120; following treatment the average reading was 117.

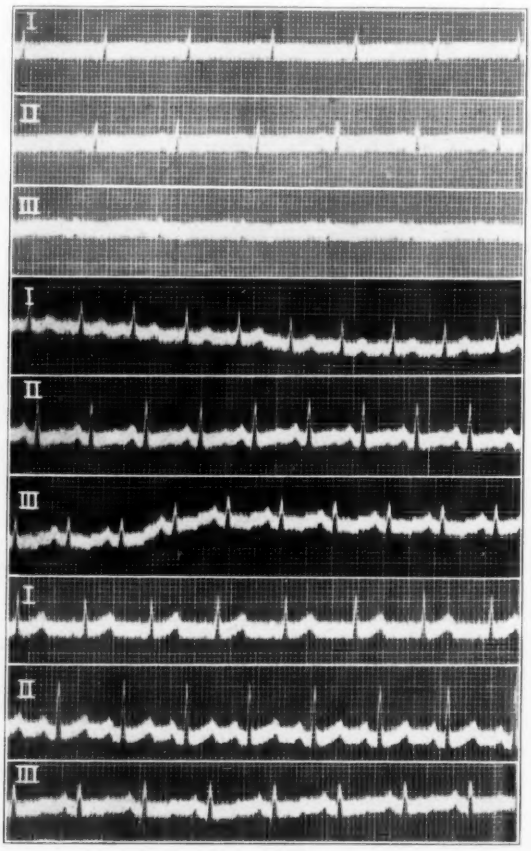

Fig. 1 (case 6).—The first set (at top) was taken before treatment; the second set fifteen days, and the last set one month, after the beginning of treatment.

Case 30 is mentioned in a separate paragraph in view of the fact that the electrocardiographic picture was different from all those studied. There was normal amplitude of all the complexes. Under intensive thyroid treatment there was a disappearance of all the symptoms of myxedema, with a corresponding rise in the basal metabolic rate and no essential change in the electrocardiographic tracing (fig. 4).

This patient first came to the clinic in 1924 for treatment of myxedema. It was not until four years later that any change in cardiac rhythm was noted. This was diagnosed as bradycardia with many extrasystoles, and the first electrocardiogram was not made until a year later;

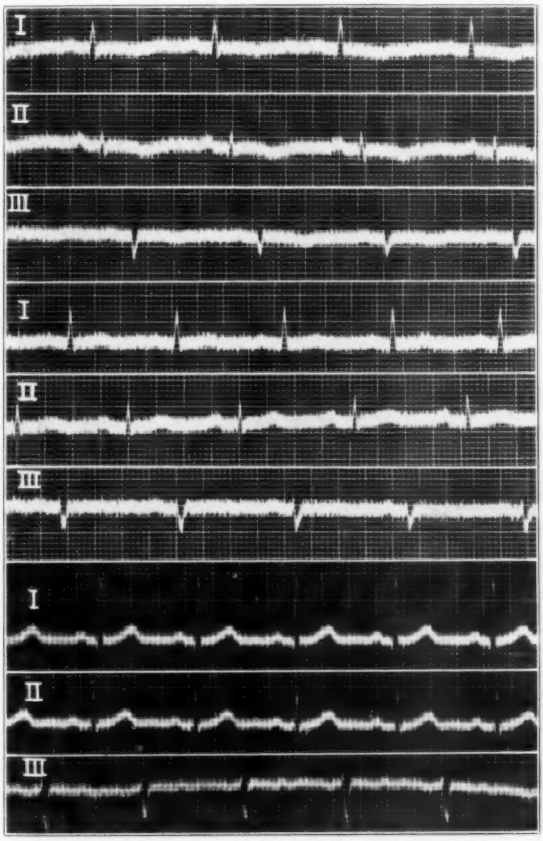

Fig. 2 (case 29).—The first set was taken before treatment; the second set six days, and the last set fifteen days, after treatment was started.

the report may be examined in table 2. At this time, in addition to thyroid medication digitalis was given, but when the fibrillation disappeared, the administration of digitalis was discontinued. However, the patient continued to show various abnormalities of rhythm, predominantly a marked sinus arrhythmia with a slow rate. Following treatment

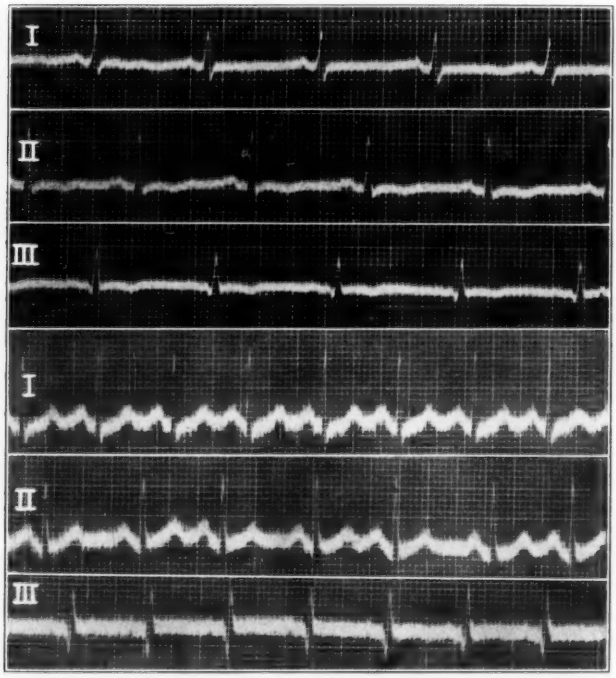

Fig. 3 (case 11).—The upper set was taken before treatment; the lower set, five months after the onset of therapy.

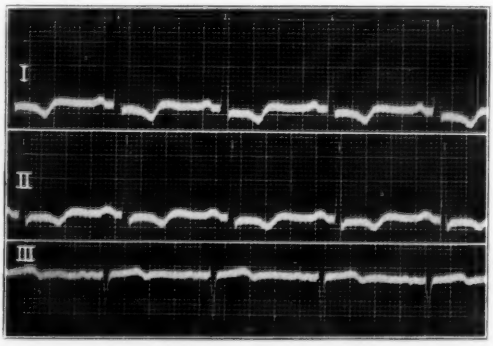

Fig. 4.—Tracings in case 30.

TABLE 2.—*Data on a Woman Aged 54 (Case 33)* *

Basal Metabolic Rate	Electrocardiograms								Roentgenogram of Heart at 7 Feet	Blood Pressure	
	Rhythm	Rate	P Waves	T_1	T_2	T_3	Axis	Ampl.	Comment		Systolic	Diastolic
—20.4	Auricular fibrillation; complete block	50	None	Norm.	Norm.	Norm.	LVP	5	Frequent premature ventricular beats	.....	148	100
	Auricular standstill	50	Norm.	Norm.	Norm.	Norm.	LVP	5	Occasional premature ventricular beats	.....	120	60
+5.1	Marked sinus arrhythmia	50	P R 12	Norm.	Norm.	Norm.	LVP	7	Q R S slurred in all leads			
	Sinus arrhythmia	40	Norm.	Norm.	Norm.	Norm.	LVP	7	Q R S slurred in all leads; premature ventricular beats; rare nodal beats			
+5.1	Probable auricular standstill with ventricular escape	33	None	Norm.	Norm.	Norm.	LVP	5	Occasional premature ventricular beats	Heart enlarged transversely; transverse diameter, 15.8		
+15	Normal sinus rhythm	60, 70	Norm.	Norm.	Norm.	Norm.	LVP	6	Frequent periods of sinus arrhythmia standstill, with ventricular escape			
+7.3	Normal sinus rhythm	86	Norm.	Norm.	Norm.	Norm.	LVP	9				
	L_1 sinus arrhythmia L_2, L_3 normal sinus rhythm	65	Norm.	Norm.	Norm.	Norm.	LVP	10	.....	Heart slightly enlarged to left transverse diameter, 12.9		
	Sinus arrhythmia	56	Norm.	———	Obscure	———	LVP	14				
	Marked sinus arrhythmia	50	Norm.	Norm.	Norm.	Norm.	LVP	9	Frequent periods of auricular standstill with ventricular escape			
	Marked sinus arrhythmia	50	Norm.	Norm.	Norm.	Norm.	LVP	7	Frequent periods of ventricular escape	Heart slightly enlarged to left		

* First electrocardiogram and blood pressure reading were obtained before treatment; all other findings, after onset of treatment. For meaning of abbreviations see table 1.

with thyroid there was a decrease in blood pressure from 148 systolic and 100 diastolic to 120 systolic and 60 diastolic.

In case 31 (table 3) in spite of the moderately low metabolic rate the patient presented a rather typical picture of myxedema. She was treated with thyroid extract. She gave a history of attacks of paroxysmal tachycardia over a period of many years, but we have no records confirming these previous seizures, and it was not until she had omitted her treatment for a period of three months that our first tracing was obtained. Four electrocardiograms were taken in the interval when she received no therapy; two of these were made during attacks of tachycardia.

It is to be noted that there was a gradual change in the T waves with a tendency toward inversion, which ultimately occurred in all the leads during the period in which the patient received no treatment. The conversion from a normal axis to a left ventricular predominance is also noted. However, no essential change was observed in the amplitude.

Eight months after reinstitution of treatment, a normal electrocardiogram and a low basal metabolic rate were obtained. Shortly following this, the patient again neglected her treatment, taking the thyroid preparation at more or less irregular intervals. The last tracing recorded shows the picture five months later, at which time she presented practically the same clinical picture of myxedema as at the onset. Unfortunately, no basal metabolic rate was obtained at this time.

According to the roentgen-ray examination, the heart was slightly enlarged when the patient had had no treatment for three months; six months later when she still received no thyroid medication it was within normal limits. A moderate hypotension was present both before and after the treatment.

GENERAL SUMMARY OF FINDINGS

Electrocardiographic Studies.—1. Incidence: There were twenty-one cases out of a total of thirty-five in which electrocardiograms were taken before treatment. Thirteen of these were of the type described by Zondek. The average age of the patients showing changes in the electrocardiogram was 47. Three cases out of the entire group developed myxedema following subtotal thyroidectomy. Two of these cases are represented in the group showing changes in the electrocardiograms and in the size of the heart.

2. Relation to Basal Metabolic Rate: With three exceptions, we found that when the basal metabolic rate dropped to a level of —25 or lower, a definitely abnormal picture was seen in the electrocardiogram. These three exceptions were basal metabolic rates of — 12, — 20 and — 22.6

TABLE 3.—*Data on a Woman Aged 39 (Case 31)* *

Basal Metabolic Rate	Electrocardiograms								Roentgenogram of Heart at 7 Feet	Blood Pressure	
	Rhythm	Rate	P Waves	T_1	T_2	T_3	Axis	Ampl.	Comment		Systolic	Diastolic
—17	.....	...	.....	.....	.....	.....	.....	..	Before treatment	.....	100	50
	Paroxysmal auricular tachycardia	200	.....	Norm.	Norm.	Norm.	Norm.	8	No treatment for 3 months	Heart and great blood vessels slightly enlarged	102	70
	Marked sinus arrhythmia	50	Norm.	Norm.	Diphasic	Inverted	Norm.	11	1 week later			
	Paroxysmal auricular tachycardia	200	.....	———	Obscure	———	LVP	8	6 months later	Heart within normal limits		
—24.5	Normal sinus rhythm	79	Norm.	Inverted	Inverted	Inverted	LVP	10	1 week later			
—30	Normal sinus rhythm	68	P_3 inverted	Norm.	Norm.	Inverted	LVP	13	8 months after treatment began			
	Normal sinus rhythm	71	Low	Low	Diphasic	Inverted	Norm.	5	Treatment irregular			

* For meaning of abbreviations see table 1.

3. Characteristics of the Tracings: In general, abnormalities noted were of the type described by Zondek.

The decreased height of the R wave was a rather constant finding. With the exception of one case in which the amplitude was artificially greater, owing to high resistance, the height was 7 mm. or less. (In the opinion of Pardee,[63] the height of the R wave varies from 7 to 16 mm. Willius [64] recorded the height as varying between 10 and 16 mm. In our series we have considered low voltage present when the R wave was less than 8 mm.) There seemed to be a parallelism between the basal metabolic rate and the height of the R wave; that is, in any one case when there was an increase in the level of the basal metabolic rate under thyroid therapy, the amplitude of the R wave increased also. However, the level of any given basal metabolic rate does not indicate the exact height of the R wave. For example, in case 20, with an initial basal metabolic rate of —59, the maximum amplitude of the R wave was 7 mm., while in case 6, with a basal metabolic rate of —43, the amplitude was 3 mm.

We denote low T waves when their amplitude is lower than 3 mm., which according to Willius is the lowest level of normalcy. Our results are tabulated as follows:

	Normal	Low	Flat	Inverted
T_1	0	1	7	5
T_2	1	2	5	5
T_3	1	1	5	6

Thus it is seen that the T waves in all leads show parallel results. It is noteworthy that the T waves in lead I were abnormal in every case. Generally speaking, the lower the amplitude of the R wave, the greater was the tendency for the T waves to be flat, and in some cases these waves, particularly in lead II, became inverted during the progress of treatment before a final rise to the upright position. In two cases the T wave in lead III, which was flat before treatment, became inverted under thyroid medication and remained so. This was probably the normal deflection for those patients. The amplitude of negative T waves in any or in all of the leads may be as much as 2 or 3 mm., even in the presence of extremely low voltage in the other waves.

Size of Heart.—Enlargement of the heart occurred in seven of the thirteen cases showing electrocardiographic changes. With one exception, the increased size of the heart was reduced as a result of thyroid therapy. The failure mentioned may be due to the fact that the treatment was carried out for only three weeks.

63. Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, New York, Paul B. Hoeber, Inc., 1928.

64. Willius, F. A.: Clinical Electrocardiograms, Philadelphia, W. B. Saunders Company, 1929.

Blood Pressure.—No characteristic changes in blood pressure were observed. In the presence of cardiac dilatation the blood pressure was found to be normal or subnormal. In those cases in which the pressure was particularly low it tended to rise under treatment. In cases in which hypertension was present the pressure tended to decrease under thyroid therapy. This last observation was made by Ohler and Ullian [65] in a previous report.

Pathologic Studies.—We have little or no pathologic material which would give us the true picture present in the heart in cases of myxedema. There was, however, one case (table 1, case 28) which presented the clinical picture of the so-called myxedema heart. The patient died an accidental death before thyroid therapy was instituted. Unfortunately, no microscopic studies were made. The heart weighed 335 Gm. There were edema of the epicardial fat and a translucent, light red heart muscle. The mitral valve showed some old thickening of the anterior flap with thickening and shortening of the chordae tendineae. The aortic arch showed irregular bands of small yellow projections running longitudinally with a few small gray-white opaque scars. The thyroid gland was represented by a thin structure separated into two lobes, almost membranous in places and without an isthmus. Section disclosed gray soft tissue having little resemblance to normal thyroid gland tissue.

Symptoms and Physical Signs.—Shortness of breath was a complaint present in almost every case of myxedema studied. Many patients complained of palpitation, and a few experienced precordial pain. These symptoms occurred as frequently in the cases not showing changes in the electrocardiogram and roentgenogram as in those that did. Edema of the lower extremities was found without respect to cardiac changes, but was more marked in the cases showing cardiac enlargement. Pulmonary congestion was found only in cases with cardiac enlargement, but this finding was not constant.

Treatment.—This consisted of administration of fresh thyroid gland extract. No attempt was made to quantify the required amount of thyroid by comparison with the metabolic rate. In general, treatment was begun slowly and was gradually increased until there was a disappearance of all symptoms subjectively and objectively, with a return to the normal picture in the electrocardigram. The last dose was considered a maintenance requirement. In some cases it was noted that the electrocardiographic changes occurred before the basal metabolic rate had risen to normal limits. In such cases it was our practice not to increase the dose in an attempt to raise the metabolic rate.

65. Ohler, W. R., and Ullian, L. J.: Clinical Survey of 1,000 Cases on Whom Basal Metabolism Studies Have Been Made, M. Clin. North America **8**:1495 (March) 1925.

COMMENT

In a review of the literature, we find numerous subjects concerning the cause of such cardiac changes as may be found in myxedema. It is our intention now to review the more important of these subjects in the light of our own study.

Changes in the Electrocardiogram.—1. Sclerosis of the Coronary Arteries: There is a very close resemblance between the variations in the electrocardiogram found in our cases of myxedema and the picture not infrequently seen in coronary sclerosis as originally described by Pardee.[16] The low voltage, the inverted T waves and the upward convexity of the S T interval are findings common to both diseases. But in our cases of myxedema, the amplitude was constantly low, while in coronary sclerosis, the height of the complexes, though frequently low, may be very high. Many of our patients showed no evidence of peripheral arteriosclerosis, and in those who did have thickened arteries there was no change in the vessels after years of treatment. The influence of arteriosclerosis is well demonstrated in one of our cases (30). In spite of the definite myxedematous syndrome, the amplitude of all the complexes was quite high, and there was marked inversion of the T waves. Had these abnormalities been due to myxedema, we should have expected to find changes, at least in the T wave, following thyroid therapy, but such was not the case. Thyroid medication had no more effect than it does on the electrocardiographic changes seen in uncomplicated coronary sclerosis. We also believe that the changes observed in the electrocardiograms of the patient referred to in table 2 were due to arteriosclerosis of the coronary arteries. Here, also, following thyroid therapy no effect was noted, not even on the bradycardia.

2. Anemia: In view of the fact that in most cases of myxedema there is at least a moderate degree of secondary anemia, the theory that the electrocardiographic changes are due to associated anemia of the myocardium cannot be dismissed lightly. Yet, according to the observations of Dr. Lawrence Ellis,[66] of the Boston City Hospital, in a series of cases of anemia no characteristic changes were noted in the electrocardiogram. Also, the results in one of our cases (34) tend to disprove the theory of anemia. On the patient's admission, the electrocardiogram showed a definitely abnormal tracing, and the blood picture was fairly normal. In the course of a few weeks there developed a well marked secondary anemia due to bleeding from the gastro-intestinal tract. Nevertheless, during this time the electrocardiogram became normal as a result of thyroid therapy. Of course, it may be argued that there is a local ischemia of the myocardium in myxedema, the determination of which is a problem yet to be solved.

66. Ellis, L. B.: Personal communication to the authors.

3. Cardiac Dilatation and Sluggishness: Can dilatation of the heart be said to account for the electrocardiographic changes? We do not believe so, in view of the fact that in several of our cases roentgenograms revealed no enlargement. Likewise, sluggishness of the myocardial contractions as a cause seems unlikely if we consider that in one of our patients the cardiac action became definitely normal as seen on fluoroscopy while there was but little change in the electrocardiogram.

4. Nervous Etiology: Vagal stimulation, which is probably a part of the general picture of myxedema, has been considered as the factor producing changes in the electrocardiogram, including prolongation of the P R conduction time. It does not seem likely, however, that alteration in nerve conduction could cause any such great degree of dilatation of the heart as we see in myxedema.

5. Cutaneous Resistance: We do not believe that resistance of the skin can result in inversion of the T waves, nor can it account for prolongation of conduction time. It is our experience that when the resistance is experimentally increased by poor electrodal contact the height of the complexes is increased rather than lowered if proper standardization is made.

6. Pericardial Effusion: Electrocardiographic changes similar to those observed in myxedema were noted in cases of pericardial effusion by Oppenheimer and Mann,[67] Master and Pardee[68] and Scherf.[69] Cases of pericardial effusion with typical coronary T waves, but without diminution of the voltage, were reported by Purks[70] and Scott, Feil and Katz.[71] Also Gordon[72] described cases of pericardial effusion showing the characteristic picture of the heart in myxedema with a return to normal following the removal of the effusion. Gager[73] has described a case (no basal metabolic studies) of pericardial effusion which showed the "myxedema tracing," together with partial heart block. Following

67. Oppenheimer, B. S., and Mann, H.: An Electrocardiographic Sign in Pericardial Effusion, Proc. Soc. Exper. Biol. & Med. **20**:431, 1922.

68. Master, A. W., and Pardee, H. E. B.: The Effect of Heart Muscle Disease on the Electrocardiogram, Arch. Int. Med. **37**:1 (Jan.) 1926.

69. Scherf, D.: Ein electrokardiographisches Zeichen bei Erguss im Herz-Beutel, Wien. klin. Wchnschr. **43**:298, 1930.

70. Purks, W. K.: The Occurrence of a Coronary T-Wave in Purulent Pericarditis, South. M. J. **24**:12, 1931.

71. Scott, R. W.; Feil, H., and Katz, L. N.: The Electrocardiogram in Pericardial Effusion, Am. Heart J. **5**:68, 1929.

72. Gordon, A. H.: Some Clinical Aspects of Hypothyroidism, Canad. M. A. J. **20**:7, 1929.

73. Gager, L. T.: Conduction Changes Accompanying Pericardial Effusion, Arch. Int. Med. **33**:449 (April) 1924.

the removal of 500 cubic centimeters of fluid from the pericardial sac, the electrocardiogram became normal, and the partial block disappeared. It is true that pericardial effusion may occur in myxedema, but it was not the cause of the changes in the electrocardiogram in our series of cases, as in only one case was there a suspicion of pericardial effusion on fluoroscopic and roentgenographic examination (case 33). Moreover, the fact that in general the cardiac pulsations return to normal under thyroid therapy with very little change in the size of the heart would seem to preclude the likelihood of the presence of an effusion.

In our opinion, none of the theories reviewed serves as an adequate explanation. Unfortunately, in our own studies, we have been unable to discover the actual underlying basis for the electrocardiographic changes. We might advance the theory already suggested, that of the presence of an actual myxedematous infiltration of the heart, a mucinous tissue involving the muscular fibers and interfibrillar spaces and nervous elements of the heart, which disappears under thyroid therapy. It may be that this abnormal tissue is present in some cases in such a small quantity as merely to produce changes in the electrical activity, evidenced by abnormalities in the electrocardiogram, without changes in the actual size of the heart, whereas in other cases there may be a sufficient quantity to cause dilatation. The test of this theory awaits more detailed pathologic study, either of man or of experimental animals.

Dangers of Treatment.—The dangers of uncontrolled thyroid treatment have been stressed by numerous writers. We should like to report here a case which has come to our attention and which, in our opinion, illustrates this point quite definitely. The patient was a man, aged 30, who when first seen had edema of the lower extremities and a basal metabolic rate of —21. He was given 15 grains (0.972 Gm.) of desiccated thyroid gland daily for the first few days, then 30 grains (1.95 Gm.) a day for a few days, and then he was allowed to go home, continuing on a dose of 15 grains (0.972 Gm.) a day. During the course of this treatment, the edema entirely disappeared. The effect of treatment in this case was not checked by electrocardiographic or metabolic studies. Four days after discharge, the patient, while at home, suddenly complained of severe pain in his left shoulder; he dropped to the floor, and in one-half hour was pronounced dead. It is our impression that this patient probably died in an attack of angina pectoris, due in part to the excessive amounts of thyroid administered.

Further dangers to be noted in the treatment of myxedema with thyroid gland extract are auricular fibrillation, as seen in a patient observed by Swan,[74] and Adams-Stokes attacks, as reported by Thomp-

74. Swan, J. M.: A Case of Auricular Fibrillation Occurring During the Administration of Thyroid Substance, Ann. Clin. Med. **3**:311, 1924.

son.[75] In both of these cases, the untoward symptoms disappeared with the diminution of the dose of the drug.

SUMMARY

1. Thirty-five cases of myxedema were studied, thirteen of which showed abnormal changes in the electrocardiogram.

2. The characteristic changes in the electrocardiogram are a decrease in voltage of all the complexes and frequently an inversion of the T waves in all the leads. Increased auricular-ventricular conduction time is seen in some cases.

3. These abnormal electrocardiograms are seen with few exceptions when the basal metabolic rate drops to a level of —25 or lower.

4. Enlargement of the heart revealed by roentgenograms is seen frequently in cases showing abnormal electrocardiograms. Sluggishness of cardiac contractions is demonstrated by fluoroscopy.

5. The specificity of thyroid gland extract in these cases is shown, the electrocardiogram and the size of the heart returning to normal following treatment.

6. Low, normal and high blood pressures are seen in myxedema. In patients with dilated hearts the pressure tends to be normal or subnormal. In our series, thyroid treatment tended to increase the blood pressures that were low and to decrease those that were high.

7. Distant heart sounds and mild congestive failure are frequent clinical findings.

8. The changes noted in this series are characteristic of the disease and warrant the use of the term, "myxedema heart."

9. Attention is directed to the paucity of careful pathologic studies of the heart muscle in myxedema. A definite explanation of the cause of the cardiac changes in myxedema may not be possible until such a study is completed.

Dr. Joseph Hallisey, in charge of the outpatient cardiac clinic, gave permission for the study of cases in his service.

75. Thompson, W.: The Blood Volume in Myxedema with a Comparison of the Plasma Volume Changes in Myxedema and Cardiac Edema, J. Clin. Investigation **2**:477, 1926.

STUDIES OF THE BLOOD IN NORMAL PREGNANCY

II. HEMOGLOBIN, HEMATOCRIT AND ERYTHROCYTE DETERMINATIONS AND TOTAL AMOUNT OF VARIATIONS OF EACH

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Many reports have been published of hemoglobin and erythrocyte determinations in pregnancy, and the accepted belief is generally that there is a decrease in both, producing an anemia which has been called the physiologic anemia of pregnancy. The hemoglobin and erythrocytes are decreased occasionally to such a degree that the anemia has been termed the pernicious anemia of pregnancy. Various theories have been advanced as to the cause of this disease. Some authors suggest excessive demands of the fetus for iron; others believe that there is a dietary cause on the part of the mother, and others that a hemolysin is produced by the syncytial cells. Irrespective of the cause of the severe anemia, the treatment is of paramount importance because the maternal and fetal mortalities are very high.

Balfour,[1] reporting 150 cases of severe anemia in pregnancy in India, stated that 42 per cent of the mothers and 68 per cent of the fetuses died. McSwiney[2] reported 43 cases, also in India, with a maternal mortality of 35 per cent and a fetal mortality of 56 per cent. Treatment has been varied, but all authors advise termination of the pregnancy. It seems strange that little or no work has been done on the etiology of a disease causing such a high mortality. The need for research in this disease is further indicated by some figures from the Chicago Lying-in Hospital. F. L. Adair instituted routine hemoglobin estimations, and in a six month period there were 1,176 new patients admitted to the clinic, of whom 268, or 23 per cent, had a hemoglobin content

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1. Balfour, M. I.: Indian M. Gaz. **62**:491, 1927.
2. McSwiney, S. A.: Indian M. Gaz. **62**:487, 1927.

under 10 Gm. The number of clinical patients with severe anemia in pregnancy is constantly increasing, owing, probably, to the economic situation. Work has been started to determine the etiology of this type of anemia.

However, before one can speak of a pernicious anemia or severe secondary anemia of pregnancy, the normal changes in hemoglobin and red blood cells incident to pregnancy must be known. All of the data which have been published, with but two exceptions, namely, those of Fehling,[3] in 1886, and of Kühnel,[4] in 1926, were obtained from a study of different groups of women during pregnancy, and because of the wide variations found normally, these data are inconclusive. Hemoglobin and hematocrit determinations and red blood cell counts on the same woman throughout pregnancy will show marked variations because of the changes in blood and plasma volumes. However, if the blood volume is determined, the total amount of hemoglobin and cells can be calculated, and the conversion of these figures to percentage of increase or decrease from certain designated standards will show definitely what effect pregnancy has on these blood constituents.

Kehrer,[5] in his review of the literature to 1923, in the Halban and Seitz system, concluded that in the healthy pregnant woman the red blood cell count, as well as the content of hemoglobin, is near the upper limits of normal, and that especially during the last month there is an additional increase. He stated the belief that this is due to increased work of the hematopoietic organs, increased intake of food and less exercise during pregnancy.

DeLee[6] stated:

> Investigators are not agreed on the changes which the blood undergoes during pregnancy and it is because the blood reacts differently under the stimulus of pregnancy in different women. From external appearances, many women, especially those ill-nourished or living in poor circumstances, suffer from a condition of chloranemia. The fetus uses up a great deal of iron and calcium, but, normally, the blood lacks neither. While in the first few months there may be a reduction in the reds, the system soon reacts to the necessities imposed by pregnancy and there is an increase of the red.

Williams[7] stated:

> In former times it was generally believed that the changes incident to the placental circulation demanded an increase in the amount of maternal blood, and

3. Fehling: Arch. f. Gynäk. **28**:453, 1896.

4. Kühnel, P.: Ztschr. f. Geburtsh. u. Gynäk. **90**:511, 1927.

5. Kehrer, E., in Halban, Joseph, and Seitz, Ludwig: Biologie und Pathologie des Weibes, Berlin, Urban & Schwarzenberg, 1926, vol. 6, p. 778.

6. DeLee, J. B.: Principles and Practice of Obstetrics, Philadelphia, W. B. Saunders Company, 1928.

7. Williams, J. W.: Obstetrics: Textbook for Use of Students and Practitioners, New York, D. Appleton and Company, 1930.

all the earlier writers stated that under the influence of pregnancy an increased hydremia and a diminution in hemoglobin and red corpuscles took place, while at the same time an abnormal amount of fibrin could be noted. These observations were based upon antiquated methods of research, and it was not until 1886 that Fehling, by the aid of modern appliances for examining the blood, came to the conclusion that it underwent little, if any, change. Since then a number of articles have appeared, notably those of Payer and Dietrich, which show that in the later months of pregnancy the amount of hemoglobin and of red corpuscles is normal, or even slightly increased. Kühnel, however, speaks of a physiological anemia of pregnancy, and believes that normal conditions are not restored until some months after delivery. Extended, but as yet unpublished, observations by Harris [8] in our service during 1922 and 1923, demonstrated that the volume of blood is definitely increased, while the cell and hemoglobin content is relatively, but not actually, diminished.

Kühnel [4] made hemoglobin, red blood cell and hematocrit determinations in 15 women throughout pregnancy and the puerperium, and in a few cases for a year post partum. His minimum figures are given in table 1. The hemoglobin determinations were made with a Sahli hemoglobinometer, which was corrected three times during the investigation, but he did not mention how it was standardized. His determinations were made on citrated venous blood which was obtained after a thirty minute rest period, without stasis. The study was carefully controlled, and we believe that it is accurate, with the one exception of the hemoglobin determinations, in which there is, according to his own statement, an average error of 10 per cent; however, his conclusions are warranted because he followed the same patients with the same methods, and the error, presumably, was constant. In all of his patients, whether they were the robust, plethoric type, or the pale, less robust type, decreasing values were found for the three factors, and the diminution was so definite that one could speak of an anemia of pregnancy. The minimum figures (decrease in hemoglobin of 20 per cent, in cell volume of 17 per cent and in erythrocytes of 20 per cent) were reached at from the sixteenth to the twenty-second week and were maintained until the thirtieth to the thirty-second week; then there was a gradual rise, reaching a maximum at about thirty-four weeks; however, the normal was not reached. He stated that pregnancy causes a slowly disappearing chlorosis that lingers for months (usually still in evidence six months post partum), and he advised a proper diet in all cases of frequently recurring pregnancies.

Plass and Bogert [9] determined the cell volume on groups of women at varying periods during pregnancy and the puerperium. Oxalate was used as an anticoagulant, and, presumably, the tourniquet was kept in place during the venipuncture. The average cell volume for nonpreg-

8. Harris, cited by Williams.[7]

9. Plass, E., and Bogert, L.: Bull. Johns Hopkins Hosp. **35**:361, 1924.

nant women was 39.5. In the first trimester it decreased to 35.6, and in the second it was 31.5, remaining at this level during the balance of the pregnancy. Three weeks post partum the cell volume was 34.7.

Skajaa [10] determined cell volumes with venous blood at term, during labor and post partum in normal and in toxemic patients, using heparin or hirudin as the anticoagulant. He summarized his report as follows: During pregnancy the cell volume diminishes. In 120 normal women at term, the mean figure was 36.4, as against a mean of 44.4 in nonpregnant women. At term and during labor the cell volume in many cases shows great variations. These are due to variations in the quantity of plasma and accordingly indicate, respectively, a condensation (concentration) or a dilution of the blood as regards suspension of erythrocytes. In women without signs of toxemia the cell volume is unchanged in the last weeks before parturition, and during labor shows little or no increase.

In 14 patients after delivery the cell volume increased steadily so that at from twelve to fourteen days post partum it was normal—43 per cent. The loss of blood, up to 350 cc., did not visibly affect the cell volume. The behavior of the cell volume in these cases may be described as representing the entirely normal manner in which the physiologic proportion between blood cells and plasma is restored after pregnancy. Twenty patients, after delivery, showed a decrease in the hematocrit reading, which was lowest on the first to the third day (usually on the second). This dilution of the blood was, in nearly all cases, far greater than would correspond to a compensation for the blood lost, and it is to be conceived as probably representing a compensation, possibly an overcompensation, for a previous concentration of the blood (during labor). Of the 20 patients with low cell volumes, after twelve days 5 had hematocrit values over 40, while the remaining 15 showed values between 38 and 40. The increase in cell volume during the puerperium may be due to the new formation of erythrocytes or to the condensation of the blood. The rapidity with which the increase takes place speaks strongly in favor of the view that it is a condensation that occurs.

Peters and Van Slyke,[11] basing their opinion on the reports of others, stated that there is a slight increase in blood and plasma volumes in pregnancy and a reduction in hemoglobin, cell volume and erythrocytes, which is somewhat too large to be explained by the hydremia. They therefore concluded that there is apparently a diminution of the body's supply of hemoglobin.

In table 1 we have listed data collected from the literature on the different constituents mentioned. The ranges and averages of the dif-

10. Skajaa, K.: Acta obst. et gynec. Scandinav. **8**:371, 1929.

11. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, vol. 1, 1931, and vol. 2, 1932.

TABLE 1.—*Averages for Hemoglobin, Hematocrit and Erythrocyte Determinations in Pregnancy*

Author	Year	Method	Hemoglobin, Gm.			Erythrocytes, Millions		Hematocrit, per Cent		
			Standard	Normal	Pregnancy, Minimum Average	Normal	Pregnancy, Minimum Average	Normal	Pregnancy, Minimum Average	No. of Determinations
Bernhard (München. med. Wchnschr. **39**: 197, 1892)....	1892	Fleischel	15.8	12.6	12.6	4.56	4.55	....	....	...
Thompson (Bull. Johns Hopkins Hosp. **15**: 205, 1904)..	1904	Gowers	....	....	65%	....	4.30	....	....	...
Gram (Ugesk. f. læger **82**: 1609, 1920).....	1920	Autenrieth-S†	13.8	11.6	10-11	....	....	36-45	....	...
		Venous blood	....	....	....	....	....	40	36	62
Kerwin and Collins (Am. J. M. Sc. **172**: 548, 1926).....	1926	Talliqvist	15.8	....	13.1	....	....	....	....	242
Kühnel [4]	1926	Sahli	17.2	15.8	12.7	....	....	39.5-44.5	....	15
		Venous blood	....	....	....	4.75	3.85	Citrate 41.5	35	...
Moore (Am. J. Obst. & Gynec. **18**: 424, 1929).....	1929	Dare	13.8	....	10.8	....	4.14	....	....	100
Jerlov (Acta obst. et gynec. Scandinav. **8**: 356, 1929)....	1929	Autenrieth-S†	Oxygen capacity	92	70%	....	....	....	....	1,143
Galloway (J. A. M. A. **93**: 1695, 1929).....	1929	Sahli	17.2	....	11.1	....	3.87	....	....	382
Bland, First and Goldstein (Am. J. M. Sc. **179**: 48, 1930)	1930	Dare	13.8	....	10.2	....	3.50	....	....	300
Harvey (Am. J. Obst. & Gynec. **21**: 476, 1931).....	1931	Sahli	17.2	....	13.8	....	3.58	....	39.8	100
		Venous blood								
Lyon (J. A. M. A. **92**: 11, 1929).....	1929	Sahli	17.2	....	12.9	....	3.51	....	....	200
Dietrich (Arch. f. Gynäk. **94**: 383, 1911).....	1911	Sahli	17.2	12	Increase	4.50	Increase	....	....	19
Skajaa [10]	1929	Venous blood	....	....	....	....	....	43-47.5	27.5-44.5	120
								44.4	36.4	
Plass and Bogert [9].....	1924	Venous blood	....	....	....	....	....	Oxalate 39.5	31.6	78

† Standardized by the oxygen capacity method.

ferent constituents are as follows: hemoglobin, from 10.2 to 13.8 Gm., average 10.8 Gm., per hundred cubic centimeters of blood; erythrocytes, from 3,500,000 to 4,550,000, average 3,910,000, per cubic millimeter, and hematocrit reading, from 31.6 to 39.8 per cent, average 35.8 per cent. It is evident that there is a lack of uniformity in the results, owing, in part, to a failure to use proper methods or apparatus. For example, only two of the investigators standardized their hemoglobinometers with the oxygen capacity method. Another factor which causes confusion is the difference in the hemoglobin standard for the different methods. Apparently three of the investigators determined red cell counts in normal

TABLE 2.—*Averages for Hemoglobin, Hematocrit and Erythrocyte Determinations in Normal Women*

	Number of Women	Standardized Method	Hemoglobin, Gm. per 100 Cc. of Blood		Hematocrit, per Cent,	Erythrocytes, Millions,
			Standard = 100%	Range Average	Range Average	Range Average
Bie and Moeller (Arch. d. mal. du cœur **15**: 177, 1922)	10	Colorimeter, oxygen	....	12.3-13.9 13.2	.... 38.7	4.25-5.21 4.74
Gram and Norgaard (J. Biol. Chem. **56**: 429, 1923)	10	Colorimeter, oxygen	13.8	12.1-14.1 13.0	38.8-43 Hirudin 40.6	4.36-5.05 4.65
Williamson (Arch. Int. Med. **18**: 505, 1916)	49	Spectrophotometer	....	15.53	....	....
Haden [14]	30	Van Slyke, oxygen	15.3*	13.34	41	4.38
Osgood and Haskins (Arch. Int. Med. **39**: 643, 1927; Laboratory Diagnosis, Philadelphia, P. Blakiston's Son & Co., 1931)	100	Colorimeter, acid-hematin, oxygen	14.3*	12-15.5 13.7	37-45 41	4.30-5.30 4.80
Wintrobe [13]	50	Newcomer, oxygen	14.2*	..... 13.76	31-41.5 39.5	4.64-5.22 4.93
Average accurate methods	278	.....	....	13.91	41.1	4.78

* Amount of hemoglobin per five million cells per hematocrit reading of 46 (Haden), 43 (Osgood and Haskins) and 42.8 (Wintrobe).

nonpregnant women as a control, and their results are therefore accurate relatively (the same error would occur in all determinations) but not absolutely, as would be the case if they had used a certified or standardized hematocytometer. Only four of the investigators determined the cell volume per hundred cubic centimeters or the hematocrit value, and yet it is the easiest and, at the same time, one of the most accurate determinations possible. Thus, it is evident that a study of the hemoglobin and hematocrit values and red blood cell count, together with determinations of blood volume, on the same women throughout pregnancy and the puerperium, with properly controlled methods, is necessary before positive statements can be made as to absolute changes in these substances.

In table 2 we have listed published data obtained with standardized methods on hemoglobin, hematocrit estimations and erythrocytes for normal nonpregnant women, together with a grand average calculated by

Wintrobe,[12] who was able to collect accurate data on only 260 women, and yet, with such a small group, we speak of a normal hemoglobin. The hematocrit values and red blood cell counts obtained by different investigators check very closely. So far as hematocrit determinations are concerned, the results are consistent, if one uses hirudin or heparin as an anticoagulant, but if one uses an electrolyte, such as citrate or oxalate, unless the solution is isotonic, one must correct for the shrinkage in cell volume (2 to 5 per cent), due to the hypertonicity of the salt. The maximum error in the hematocrit determinations is 2 per cent of the reading. The red cell counts, if made with a certified pipet and hematocytometer, have an error of 5 per cent. Likewise, the aver-

TABLE 3.—*Methods for Determination of Hemoglobin and Probable Errors*

		Volume of Blood	Probable Error, per Cent*	Standard, Gm. per 100 Cc. Blood
Williamson	Spectrophotometer, pure hemoglobin	Drop	1	....
Van Slyke	Oxygen capacity	1 to 2 cc.	0.5	....
Van Slyke	Carboxyhemoglobin	1 to 2 cc.	0.5	....
Haldane-Palmer	Colorimeter, carboxyhemoglobin	0.1 to 0.5 cc.	1 to 2	13.8
Osgood and Haskins	Colorimeter, acid-hematin	1 cc.	1 to 2	13.8
Newcomer	Colorimeter, plate	0.02 cc.	5 to 40	16.9
Wintrobe	Colorimeter, plate	.....	3 †	....
Sahli, original	Colorimeter	0.02 cc.	25 to 40	17.2
present	.....	.....	.....	14.0
Dare, prior to 1926	Colorimeter	Drop	20 to 40	13.8
1931	Colorimeter	.....	.....	16.0
Tallqvist	Colorimeter, paper	Drop	20 to 40	15.8

* According to F. Schwentker.
† Newcomer plate with 19 per cent error; correction curve reduced error to 3 per cent.

age hemoglobin per hundred cubic centimeters of blood lies between certain narrow limits, but when one notes the various methods used to determine hemoglobin content (table 3) and the inherent errors of each, as determined by Schwentker,[13] Wintrobe,[12] Haden,[14] and others, one no longer wonders at the marked discrepancies in reports on hemoglobin determinations.

The standards of all methods for determining hemoglobin are based on the oxygen capacity, if the hemoglobin is normal. Many colorimetric methods will give exact results, but if the hemoglobin is abnormal (e. g., methemoglobin) high readings will be obtained with all methods, except with the oxygen capacity method. In a recent case report on

12. Wintrobe, M. M.: Blood of Normal Young Women Residing in a Subtropical Climate, Arch. Int. Med. **45**:287 (Feb.) 1930.
13. Schwentker, F. F.: J. Lab. & Clin. Med. **15**:247, 1929.
14. Haden, R. L.: Folia haemat. **31**:113, 1925.

methemoglobinemia in pregnancy, one of us (W. J. D.) [15] pointed out certain errors that can occur in determinations on patients with abnormal hemoglobin. Therefore, finding the oxygen capacity is the ideal method, but it requires fifteen minutes or longer for a single determination, and we believe, because of the daily variations which we have found to be as much as 10 to 15 per cent, that a large number of determinations with a fairly accurate procedure are of far greater value than a few with the highest degree of accuracy. Of the numerous methods with which hemoglobin can be accurately determined by a short colorimetric procedure, that of Palmer,[16] in which it is determined as carbon monoxide hemoglobin, has been used by us since 1924, and it is noteworthy that Peters and Van Slyke,[11] in their monograph on biochemical methods, give precedence to this method above other colorimetric procedures. It has an error of less than 2 per cent. For purposes of comparison and for clearness, we are reporting our results in grams of hemoglobin per hundred cubic centimeters of blood. The figures for oxygen capacity can be obtained by multiplying the grams of hemoglobin by 1.34 (1 Gm. of hemoglobin theoretically combines with 1.34 cc. of oxygen).

METHOD

Studies were made on venous blood taken after at least a twenty minute period of rest, if the patient was ambulatory, without stasis, using heparin as an anticoagulant (heparin does not affect the size or volume of cells). Erythrocyte counts were made with a Bureau of Standards certified pipet and hematocytometer. Hematocrit determinations were made in Plass hematocrit tubes and hemoglobin determinations were made with the Palmer carbon monoxide hemoglobin method, in a few of the early cases with 0.2 cc. of blood diluted to 20, and in the remainder with 0.5 cc. diluted to 50. All of the pipets were either certified or calibrated in the laboratory. The hemoglobin standards were made up fresh each week from a standard with a known oxygen capacity. The oxygen capacity of the blood of one of the patients was determined each week as an additional control of the standard. Determinations of blood and plasma volume, as described in the preceding report,[17] were made in addition. The means for the total number of cases are based on all of the patients studied, for series A on the patients followed throughout pregnancy and the puerperium, and for series B, on those followed from late pregnancy to eight weeks post partum.

In table 4 are listed the variations and averages in hemoglobin per hundred cubic centimeters of blood for the entire series throughout pregnancy and the puerperium. For the first trimester the mean for the total cases was based on the patients whose hemoglobin was within the normal range, namely, from 11 to 16.5 Gm. All other means are

15. Dieckmann, W. J.: Methemoglobinemia in Pregnancy, Arch. Int. Med. **50**:574 (Oct.) 1932.

16. Palmer, W. W.: J. Biol. Chem. **33**:119, 1918.

17. Dieckmann, W. J., and Wegner, C. R.: The Blood in Normal Pregnancy: I. Blood and Plasma Volumes, Arch. Int. Med. **53**:71 (Jan.) 1934.

based on all of the estimations for hemoglobin, unless the patient had a hemorrhage or the findings were obviously abnormal. While these variations of the mean seem marked, mathematically, the difference between the various means for the different periods of pregnancy is insignificant. However, in series A and B, in which the same patients are followed, the changes are of significance. In series A the hemoglobin is slightly below normal (14.3 Gm. per hundred cubic centimeters of blood) at from ten to fifteen weeks' gestation; it decreases still more at from twenty-six to thirty-five weeks to a figure which is 15 per cent below normal; it increases slightly at term, decreases after delivery, and at two weeks post partum it is still 17 per cent

TABLE 4.—*Hemoglobin, Grams Per Hundred Cubic Centimeters of Blood: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
Hemoglobin, Gm. per 100 Cc.	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 25	8 to 17 Weeks
6.9- 9.9	..	..	3	2	4	6	1
10.0-11.9	5	1	5	10	6	8	2
12.0-13.9	10	4	14	31	12	12	6
14.0-15.9	9	3	3	10	3	4	2
16.0-17.3	2	..	1	2	..	2	..
Total	26	8	26	55	25	32	11
			Mean				
Total cases	13.6 ± 0.23	.....	12.5 ± 0.25	13.0 ± 0.15	12.1 ± 0.24	11.9 ± 0.24	12.5 ± 0.43
Standard deviation	1.73	....	1.86	1.62	1.80	2.00	2.10
Series A	13.80	.....	12.20	12.40	.....	11.78	
Series B	.....	.....	.....	12.0	11.6	11.1	

below normal. In series B the hemoglobin at term is 15 per cent below normal, and at eight weeks post partum it is still 14 per cent below normal. Our data also show the wide range of hemoglobin in normal pregnant women and reveal that in some patients it may be from 30 to 50 per cent below the normal, without the occurrence of any symptoms or signs. The patients were all from the clinic; they were not selected, and yet only 5 had an initial hemoglobin content less than 11 Gm. (7.7, 7.8, 9.0, 9.3, 10.6). The initial hemoglobin content was normal in 6 patients, but decreased markedly during pregnancy, the minimum figures varying from 9 to 11 Gm. Seven patients had normal amounts of hemoglobin ante partum, but decreased amounts post partum, the figures varying from 7 to 11 Gm.

Dreyer and his co-workers [18] and Rabinowitch [19] have made hourly or bi-hourly determinations of the hemoglobin content of the blood of

18. Dreyer, G.; Bazett, H., and Pierce, H.: Lancet **2**:588, 1920.
19. Rabinowitch, I. M.: J. Lab. & Clin. Med. **9**:120, 1923.

adults throughout the day, and they agree in concluding that in a given subject the difference between the lowest and highest hemoglobin content observed during the same day may amount to from 20 to 30 per cent of the average content. Peters and Van Slyke stated that Mackay and Hiller have observed a fairly steady change in hemoglobin content during the day in the blood of laboratory workers, with differences as great as 1.5 Gm. of hemoglobin. They believe that variations of from 20 to 30 per cent appear to be rare in the resting or only moderately active person. Smith [20] stated that variations of hemoglobin and erythrocyte determinations are within the limit of error for hourly observations during an eight hour period, that food, rest or moderate activity causes no significant variations and that there may be real differences on different days or over a long period. Unpublished work of ours, in which we determined the oxygen capacity, carboxyhemoglobin and hematocrit value on seven persons, indicates that the hemoglobin may vary from 1 to 15 per cent during the forty-eight hour study, with the subject carrying on his usual work. Since Jan. 30, 1928, the hemoglobin content of one of us (W. J. D.) has been determined twenty-five times and, with but one exception, has ranged from 16 to 18.4 Gm., but the majority of the readings have been 17.5 ± 1 Gm. During the forty-eight hour study the hematocrit was remarkably constant, all readings checking within less than 3 per cent.

In table 5 are listed a series of hemoglobin, hematocrit and serum protein determinations during labor and the early puerperium. With the exception of patient 60, there were marked variations in hemoglobin, but there were changes of the same magnitude in hematocrit estimations, blood and plasma volumes and serum protein, thus indicating that the variations are due to concentration or dilution of the blood. It is evident that hemoglobin, hematocrit or erythrocyte determinations during labor or within twenty-four hours post partum are of comparatively little value in ascertaining whether or not the patient has normal blood. Keith,[21] in wounded soldiers, found variations as great as 40 per cent in blood volume and in hemoglobin and hematocrit determinations within a period of a week, owing to replacement of volume with, primarily, water (plasma), but there was also a more rapid increase in cells than it would conceivably be possible to manufacture, suggesting that in conditions in which the blood volume fluctuates, the

20. Smith, C.: Normal Variations in Erythrocyte and Hemoglobin Values in Women, Arch. Int. Med. **47**:206 (Feb.) 1931.

21. Keith, N. M.: Blood Volume Changes in Wound Shock and Primary Haemorrhage, Medical Research Committee Special Report no. 27, London, His Majesty's Stationery Office, 1919.

TABLE 5.—*Variations in Hemoglobin, Hematocrit, Serum Protein and Blood Volume During Labor and the Puerperium*

Number, Gravida, Color, Age	Date	Comment	Hemoglobin, Gm. per 100 Cc.	Hematocrit, per Cent	Blood Volume, Cc.	Plasma Volume, Cc.	Serum Protein, per Cent	Erythrocytes, Millions
60	5/12	Late in labor	12.5	38	4,822	2,990	6.7	4.38
I		1.5 hrs. pp.†	11.5	36	100 cc. blood loss		6.1	
C*		6 hrs. pp.	11.0	36	.....	.....	5.6	
23	5/13	12 hrs. pp.	11.0	36	5,318	3,404	5.9	
		24 hrs. pp.	11.0	34	.....	.....	5.7	
	5/14	48 hrs. pp.	11.0	35	.....	.....	6.3	
	5/15	72 hrs. pp.	11.0	35	4,687	3,047	5.5	3.47
38	3/ 6	.....	12.5	36	5,617	3,595	6.0	4.49
VI	3/10	.....	14.5	40	.....	.....	6.6	
C	3/17	Early in labor	15.3	41	.....	.....	6.6	
27		Late in labor	16.2	42	150 cc. blood loss		7.1	
		1 hr. pp.	15.7	41	.....	.....	6.6	
		6 hrs. pp.	13.8	42	.....	.....	6.4	
	3/18	12 hrs. pp.	13.4	40	5,176	3,106	6.2	3.79
		24 hrs. pp.	13.1	39	.....	.....	5.8	
	3/19	48 hrs. pp.	13.1	38	.....	.....	6.5	
	3/20	72 hrs. pp.	13.8	39	4,483	2,735	6.7	3.86
	4/ 8	24 days	12.5	36	3,975	2,544	6.3	4.14
58	11/20	.....	13.1	39	6,557	4,000	6.2	4.26
I	11/25	Late in labor	11.5	39	100 cc. blood loss		6.4	
W		1 hr. pp.	12.0	38	.....	.....	6.3	
20	11/26	6 hrs. pp.	9.2	30	.....	.....	5.7	
		12 hrs. pp.	10.6	..	.....	.....	5.1	
		24 hrs. pp.	13.1	37	.....	.....	6.0	
	11/28	60 hrs. pp.	12.0	36	.....	.....	6.1	
	11/29	84 hrs. pp.	11.5	34	4,545	3,000	6.2	3.98
	12/ 6	.....	12.0	34	5,612	3,704	...	3.86
	1/28	8 wks.	14.5	40	.....	.....	6.9	
34	12/18	.....	14.5	40	6,000	3,600	6.6	4.50
I	1/13	Early in labor	13.1	40	.....	.....	6.3	
C	1/15	Late in labor	15.3	44	550 cc. blood loss		7.1	
25		1 hr. pp.	13.1	39	.....	.....	6.1	
		6 hrs. pp.	11.5	36	.....	.....	6.3	
	1/16	12 hrs. pp.	12.0	37	4,161	2,622	6.2	3.97
		24 hrs. pp.	11.0	34	.....	.....	5.8	
	1/17	48 hrs. pp.	12.0	34	.....	.....	5.4	
	1/19	82 hrs. pp.	11.0	32	.....	.....	6.0	
	1/20	5 days	11.5	33	3,876	2,597	5.9	4.06
	3/11	8 wks.	12.0	39	5,193	3,168	7.3	4.28

* C indicates colored race; W, white race.
† pp. indicates post partum.

TABLE 6.—*Hemoglobin in Grams per Kilogram of Body Weight: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
Hemoglobin, Gm. per Kg.	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 25	8 to 17 Weeks
4.0- 5.9	..	..	1	1	3	3	..
6.0- 7.9	6	..	4	6	6	8	1
8.0- 9.9	7	3	8	16	4	7	1
10.0-11.9	3	3	9	19	10	5	2
12.0-13.9	6	2	2	12	1	7	4
14.0-15.9	3	..	2	..	..	1	1
16.0-18.2	1	..	..	..	1	1	1
Total	26	8	26	54	25	32	11
			Mean				
Total cases	10.3 ± 0.42	.....	10.0 ± 0.31	10.3 ± 0.18	9.1 ± 0.42	9.8 ± 0.38	
Standard deviation	3.14	....	2.36	2.02	3.10	3.18	
Series A	10.52	.....	9.28	9.15	9.93	10.90	
Series B	.....	.....	....	9.82	8.7	7.9	9.53

body either holds or builds up a store of reserve cells in the spleen, liver, mesenteric capillaries, and other parts. Gross fallacies in the erythrocyte counts are particularly evident (patient 60).

In table 6 are listed the variations and averages of the grams of hemoglobin per kilogram of uncorrected body weight. The total amount of hemoglobin was obtained by multiplying the grams of hemoglobin per hundred cubic centimeters by the blood volume in cubic centimeters, divided by 100. The grams per kilogram were then obtained by dividing the total hemoglobin by the weight. The normal amount of hemoglobin per kilogram, according to the data of Rowntree and Brown,[22] is 12 Gm. In pregnancy there are marked variations with a decided tendency toward low values. The means for the different periods of the total cases show no significant change. Series A shows a decrease in grams of hemoglobin per kilogram throughout pregnancy, reaching a minimum at term and returning to normal at from ten to fifteen days post partum. Series B shows an average which is lower than the general average at term, with a 20 per cent additional decrease at from ten to fifteen days, and a figure at eight weeks which is still a little below that of the figures for term. It would seem that as the weight (a considerable portion of which is actual maternal tissue requiring adequate blood supply) increases in pregnancy, the body attempts to maintain a constant amount of hemoglobin per kilogram, but after delivery this mechanism does not seem to function so well (lactation?), and at eight weeks post partum the amount of hemoglobin per kilogram is still decidedly below normal. It is also evident from the data that many parturient women go through pregnancy with very low amounts of hemoglobin per kilogram, but relatively normal amounts of hemoglobin per hundred cubic centimeters, and this deficiency may explain certain of the obscure cases of obstetric shock, infection and death.

In table 7 are listed the variations and averages for the hematocrit determinations in pregnancy and the puerperium. The majority of the figures are between 33 and 42 per cent, but the number of low cell volumes increases during pregnancy and especially post partum. There are no significant differences between the means of the total number of cases, but the changes in series A and B are of significance because the same patients were followed. In series A the average hematocrit value is 7 per cent below normal (43) in the first trimester, 14 per cent in the second and 11 per cent at term, and at two weeks post partum it is still 6 per cent below normal. The hematocrit value in series B at from ten to fifteen days is 16 per cent, and at eight weeks it is still 13 per cent below normal. Several explanations of this

22. Rowntree, L. G., and Brown, G. E.: Volume of the Blood and Plasma, Philadelphia, W. B. Saunders Company, 1929.

decrease in the hematocrit value are possible: (1) The cells decrease in size; (2) there is a greater increase in plasma than in blood volume, and (3) there is an actual decrease in the total number of cells. The individual cell volumes have been determined and found to be normal or even a little larger than normal. Our averages for changes in blood and plasma volume show that there is only a slightly greater increase in plasma than in blood, but a study of individual patients in table 9 indicates that the increase in plasma is usually greater than the increase in blood; therefore, the cell volume is diminished. Data for changes in total amount of erythrocyte mass prove that there is a definite increase,

TABLE 7.—*Percentage of Hematocrit: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
Hematocrit, per Cent	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 25	8 to 17 Weeks
22-27	..	..	1	..	2	2	..
28-32	..	..	3	5	3	4	1
33-37	7	2	9	14	10	7	2
38-42	14	6	12	33	8	14	8
43-47	5	1	..	3	2	4	..
48-52	..	..	1	1	..	1	..
Total	26	9	26	56	25	32	11
			Mean				
Total cases	39.6 ± 0.44	....	36.9 ± 0.55	38.3 ± 0.35	36.0 ± 0.52	37.7 ± 0.66	38.2 ± 0.65
Standard deviation	3.35	....	4.18	3.93	3.88	5.53	3.22
Series A	39.8	....	36.9	38.1	38.0	40.1	
Series B	....	....	....	37.6	36.0	35.6	

but it is not equal to the increase in plasma; consequently the cell volume is relatively, but not actually, diminished.

In table 8 are listed the variations and averages of erythrocyte counts during pregnancy and the puerperium. The wide range, with the lower figures increasing in number toward term, is noteworthy, but the striking fact is the rapid return to normal post partum. The erythrocyte counts in the first trimester are normal, decrease during the period from the twenty-sixth to the thirty-fifth week, increase at term and decrease during the first post partum week, but are normal at three weeks post partum. The difference of the means for the first period and for the period of from twenty-six to thirty-five weeks is of significance. Series A and B show similar changes. Thus it is evident that the number of erythrocytes per cubic millimeter decreases in pregnancy, but that post partum the body is able to manufacture red blood cells but is not able to replace the hemoglobin as rapidly as the cells. The number of cells is relatively but not actually decreased. An expla-

nation similar to that given for variations in hematocrit readings explains this phenomenon. (The hematocrit value is measured as the cubic centimeters of cells per hundred cubic centimeters of blood, and the erythrocyte counts are measured as the number of cells per cubic millimeter. Thus the determinations are similar, but differ in the unit used.)

The changes in hemoglobin, hematocrit and erythrocyte determinations are even more evident in individual patients than in the group. It is impossible to list all of the data, but in table 9 are grouped normal patients (series A) in whom repeated determinations were made throughout pregnancy and the puerperium. The majority of the patients show a decrease in hemoglobin, hematocrit and erythrocyte determi-

TABLE 8.—*Erythrocytes, Millions per Cubic Millimeter: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
Erythrocytes, Millions	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
3.0-3.4	..	..	2	2	6	5	..	..
3.5-3.9	2	1	16	10	8	5	2	..
4.0-4.4	15	5	5	28	10	12	4	6
4.5-4.9	4	3	..	12	1	4	4	4
5.0-5.4	4	..	1	1	..	2	..	1
Total	25	9	24	53	25	28	10	11
			Mean					
Total cases	4.45 ± 0.067	.....	3.88 ± 0.05	4.25 ± 0.037	3.87 ± 0.06	4.12 ± 0.07	4.34	
Standard deviation	0.425	.....	0.386	0.40	0.413	0.56		
Series A	4.38	.....	3.91	4.20	3.85	4.24		
Series B	....	.....	....	4.23	3.98	4.34	....	4.44

nations during pregnancy, and an increase post partum. The amount of hemoglobin and cells per kilogram tends to remain fairly constant during pregnancy. Furthermore, the majority of the patients weigh more after pregnancy than they did before, and therefore require more blood. Likewise, many patients begin pregnancy with a subnormal hemoglobin content and cell volume, and although the total amount after delivery is greater than that found early in pregnancy, it is still below normal. In patients 1, 2, 3, 5, 12 and 13, especially, marked changes occurred during pregnancy and the puerperium and in patient 7 during the puerperium. Tables 9 and 10 demonstrate the fallacy of erythrocyte determinations, even with certified apparatus. That is, the cell count in pregnancy is no index of the amount of hemoglobin and may actually be misleading (patients 1, 3, 8, 12 and 53). Since the cell is only a vehicle for hemoglobin, more time and care should be devoted to determining the latter. In fact, unless the volume of the individual cell is in question, erythrocyte counts should be discarded completely.

TABLE 9.—*Data on Patients Followed Throughout Pregnancy and the Puerperium (Series A)* *

Number, Gravida, Color, Age	Period of Gestation or Post Partum	Weight, Kg.	Hemoglobin				Volume Change		Hematocrit			Erythrocytes, Millions per C.Mm.
			Gm. per 100 Cc.	Gm. per Kg.	Total Amount, Gm.	Change, per Cent	Blood, per Cent	Plasma, per Cent	Change, per Cent	Total Volume, Cc.	Per Cent	
			1	2	3	4	5	6	7	8	9	10
1	13 wks.	46.3	13.8	9.3	429	...	...	...	...	1,245	40	4.66
II	29 wks.	55.9	12.5	11.2	627	146	160	166	153	1,903	38	3.86
W†	40 wks.	59.5	10.2	10.2	605	141	190	206	161	2,075	35	4.00
20	12 days	50.4	11.4	12.5	633	105	93	90	99	2,042	37	4.31
2	14 wks.	77.9	11.9	7.0	545	...	...	...	...	1,650	36	4.28
I	30 wks.	81.0	10.6	6.5	527	97	108	115	96	1,584	32	3.39
W	40 wks.	80.9	9.1	5.6	452	83	109	119	90	1,490	30	3.45
23	12 days	73.6	11.0	7.0	512	113	93	86	109	1,625	35	4.05
3	15 wks.	53.0	16.3	16.0	850	...	...	...	...	2,245	43	4.47
I	30 wks.	61.1	14.5	15.2	930	109	123	125	120	2,693	42	3.79
W	40 wks.	63.5	10.6	9.1	577	68	104	116	89	2,004	37	3.90
23	12 days	53.0	17.3	18.2	968	168	103	91	123	2,464	44	....
4	14 wks.	92.2	15.3	8.9	823	...	...	...	...	2,362	44	5.26
VII	27 wks.	91.7	14.5	10.0	976	111	118	122	112	2,649	42	4.89
W	40 wks.	87.0	14.5	11.9	1,036	126	133	133	133	3,143	44	....
30	14 days	82.7	14.2	9.9	817	79	81	75	88	2,760	48	5.38
5‡	12 wks.	53.6	14.5	10.0	534	...	...	...	...	1,546	42	4.52
II	28 wks.	59.5	12.4	9.3	552	103	121	129	109	1,690	38	4.14
W	39 wks.	60.0	11.4	9.2	552	103	131	140	119	1,832	38	4.28
25	14 days	52.5	9.7	10.9	573	104	123	123	123	2,254	38	3.94
6	14 wks.	45.9	11.4	8.6	393	...	...	...	...	1,237	36	4.06
I	27 wks.	54.8	12.5	10.1	554	141	129	125	137	1,690	38	3.90
W	40 wks.	63.5	12.5	10.0	634	161	148	141	160	1,985	39	5.02
19	11 days	56.0	15.3	13.7	768	121	99	94	106	2,106	42	4.59
7	14 wks.	107.2	13.1	7.0	754	...	...	...	...	2,302	40	3.76
VI	30 wks.	112.5	12.5	6.6	741	98	103	110	93	2,127	36	3.87
W	40 wks.	114.6	13.1	7.4	848	112	112	112	113	2,588	40	4.09
31	5 days	100.3	12.5	7.8	784	92	97	103	87	2,250	36	3.37
	13 days	100.4	12.5	9.8	983	116	121	127	112	2,900	37	3.07
8	14 wks.	92.9	13.5	9.6	889	...	...	...	...	2,325	35	4.13
III	28 wks.	103.5	13.1	8.0	822	92	95	92	100	2,319	37	3.76
C	40 wks.	108.9	13.1	8.5	924	104	106	100	117	2,749	39	4.45
30	11 days	100.0	9.5	5.1	514	56	77	85	63	1,726	32	4.00
9	14 wks.	50.0	11.5	9.1	455	...	...	...	...	1,468	37	3.99
I	29 wks.	58.8	12.0	9.8	576	126	121	127	111	1,632	34	3.58
C	40 wks.	60.0	12.0	10.4	625	137	131	129	135	1,977	38	4.08
21	3 days	55.8	12.5	11.0	615	99	94	94	94	1,867	38	4.00
	12 days	52.5	13.8	13.4	704	113	98	92	108	2,144	42	4.19
10	20 wks.	71.8	13.8	10.3	735	...	...	...	...	2,136	40	4.34
I	36 wks.	75.5	16.2	12.2	1,040	142	120	113	132	2,828	44	4.91
W	3 days	70.3	14.5	11.0	768	74	83	88	99	2,120	40	4.18
26												
11	15 wks.	67.2	14.1	12.2	822	...	...	...	...	2,390	41	4.23
I	28 wks.	73.8	11.4	8.9	660	80	99	102	94	2,247	39	4.42
W	39 wks.	76.5	12.0	9.1	692	84	99	102	94	2,247	39	4.52
22	12 days	68.1	13.8	12.4	842	122	106	94	125	2,809	46	4.43
12	9 wks.	61.3	14.9	12.7	776	...	...	...	...	2,137	41	5.33
I	27 wks.	80.0	8.2	6.9	552	71	130	133	125	2,681	31	3.73
C	40 wks.	86.3	12.2	6.9	595	77	94	102	83	1,764	36	4.08
28	11 days	75.6	11.0	7.2	546	92	101	98	107	1,885	38	4.41
13	11 wks.	68.1	15.3	13.9	946	...	...	...	...	2,590	42	....
VIII	29 wks.	75.4	11.4	9.2	692	73	98	106	86	2,237	37	3.65
C	40 wks.	71.5	11.0	8.6	613	65	90	99	77	1,999	36	3.64
37	11 days	65.6	13.8	12.0	786	128	102	92	120	2,388	42	....
22	16 wks.	55.7	13.8	12.4	690	...	...	...	...	2,000	40	4.09
II	28 wks.	64.3	13.1	9.1	585	85	89	95	80	1,605	36	3.82
W	40 wks.	67.5	12.5	....	...	...	...	...	...	.....	39	....
24	12 days	60.8	13.1	9.5	577	99	99	93	110	1,762	41	....

* Loss of blood at delivery, unless excessive or measured, is assumed to be approximately 200 cc.

† In this table, W indicates white race; C, colored race.

‡ Patient 5 had a cesarean section.

In table 10 essential data on series B are given. All but 2 of the patients at eight weeks post partum had hemoglobin and hematocrit values equal to or exceeding those found at term, but still below normal. The red blood cell counts show marked increases, so that at from ten

TABLE 10.—*Data on Patients Followed From Term to Eight Weeks Post Partum (Series B)* *

			Hemoglobin				Volume Change		Hematocrit			
Number, Gravida, Color, Age	Period of Gestation or Post Partum	Weight, Kg.	Gm. per 100 Cc.	Gm. per Kg.	Total Amount, Gm.	Change, per Cent	Blood, per Cent	Plasma, per Cent	Change, per Cent	Total Volume, Cc.	Per Cent	Erythrocytes, Millions per C.Mm.
			1	2	3	4	5	6	7	8	9	10
31	39 wks.	67.0	12.3	11.8	790	...	...	...	...	2,557	39	4.62
I	12 days	56.5	13.8	10.8	610	77	67	64	73	1,855	42	5.06
C†	8 wks.	53.6	15.3	15.2	815	103	81	74	91	2,339	44	4.98
15												
32*	40 wks.	65.0	13.1	11.2	727	...	...	...	...	2,222	40	4.07
I	3 days	58.0	10.9	7.1	413	57	68	77	55	1,212	32	3.29
W	12 days	55.5	10.4	8.0	443	61	77	82	69	1,542	36	4.32
27	8 wks.	60.5	13.8	10.4	628	86	82	82	82	1,818	40	5.09
33	40 wks.	103.4	11.0	6.1	630	...	...	...	...	1,824	32	3.32
II	3 days	90.0	12.0	7.9	712	113	104	98	117	2,137	36	4.20
W	19 days	87.5	12.0	7.4	648	103	95	89	107	1,942	36	4.58
29	9 wks.	89.2	12.0	8.2	734	117	107	104	114	2,079	34	4.06
35*	36 wks.	68.1	11.4	8.6	582	...	...	...	...	1,932	38	4.31
I	11 days	61.5	10.6	7.1	434	75	80	88	68	1,308	32	4.03
W	8 wks.	58.6	11.6	8.5	496	85	84	84	84	1,626	38	4.48
24												
36	40 wks.	68.4	9.3	6.3	430	...	...	...	...	1,487	32	3.74
I	3 days	63.0	6.9	5.1	324	75	101	110	82	1,221	26	3.33
C	12 days	56.8	8.2	5.2	295	69	78	86	61	907	25	3.11
25	8 wks.	54.5	8.2	6.7	363	84	96	100	87	1,291	29	4.09
37	38 wks.	82.0	11.0	10.6	869	...	...	...	...	2,990	38	4.37
III	12 days	73.0	11.0	6.6	479	55	61	60	62	1,866	39	4.50
W	8 wks.	75.0	11.0	9.4	706	81	81	85	75	2,237	35	4.59
30												
39	39 wks.	62.5	14.0	11.6	785	...	...	...	...	2,356	42	4.49
I	11 days	51.9	12.6	9.8	455	58	64	67	61	1,445	40	4.39
W	17 wks.	50.0	13.8	6.4	438	56	57	59	54	1,272	40	4.57
17												
40	40 wks.	54.0	11.0	9.4	505	...	...	...	...	1,650	36	4.39
III	3 days	48.2	13.8	13.9	670	133	106	96	124	2,044	42	4.56
C	25 days	46.8	13.1	12.8	600	119	100	100	99	1,635	36	4.44
28	8 wks.	47.2	12.6	10.4	490	97	85	82	89	1,475	38	4.12
43	38 wks.	72.2	12.6	10.6	765	...	...	...	...	2,372	39	4.51
I	5 days	63.5	14.5	11.2	707	92	80	71	95	2,242	46	4.44
C	19 days	62.2	13.8	15.6	970	127	115	110	124	2,953	42	4.79
17	8 wks.	61.9	12.6	10.4	695	91	84	86	82	1,945	38	4.13

* Patients 32 and 35 had losses of blood amounting to 1,020 cc. and 400 cc. ±, respectively; the other patients had losses of from 50 to 200 cc.±

† In this table, W indicates white race; C, colored race.

to fifteen days they were normal, indicating that the hematopoietic tissue was able to form erythrocytes but not to give them their normal amount of hemoglobin. Patient 32 had a measured blood loss of 1,020 cc., which was reflected in a 32 per cent decrease in blood volume and a 43 per cent decrease in total hemoglobin, but only a 17 per cent decrease

in grams of hemoglobin per hundred cubic centimeters of blood. The recovery was extremely rapid, and at eight weeks the hemoglobin was essentially normal when calculated on the basis of both volume and weight. Patient 36 was first seen at term with a definite anemia, which

TABLE 11.—*Average Changes in Hemoglobin and Total Cell Mass Calculated from Variations in Total Amount, Using the Initial Determination As 100 Per Cent for the Antepartum Period*

	Hemoglobin		Cell Mass	
	Number of Cases	Mass Change, per Cent	Number of Cases	Mass Change, per Cent
From 26 to 35 weeks of gestation:				
Average increase for all patients	17	5.8	17	10.4
Average increase for those showing increase	7	33.0	9	27.1
Average decrease for those showing decrease	6	21.4	5	13.0
No change	4	0	3	0
From 36 to 40 weeks of gestation:				
Average increase for all patients	14	13.0	14	19.9
Average increase for those showing increase	7	42.7	9	38.4
Average decrease for those showing decrease	5	24.6	5	13.4
No change	2	0	..	0

TABLE 12.—*Average Changes in Hemoglobin and Total Cell Mass Calculated from Variations in Total Amount, Using the Last Antepartum Determination As 100 Per Cent for the Post Partum Period*

	Hemoglobin		Cell Mass	
	Number of Cases	Mass Change, per Cent	Number of Cases	Mass Change, per Cent
From 2 to 6 days post partum:				
Average decrease for all patients	24	17.3	24	15.2
Average decrease for those showing decrease	18	26.8	16	26.6
Average increase for those showing increase	3	23.0	3	22.3
No change	3	0	5	0
From 10 to 25 days post partum:				
Average decrease for all patients	40	8.3	40	10.5
Average decrease for those showing decrease	25	25.4	23	27.1
Average increase for those showing increase	11	26.4	13	15.7
No change	4	0	4	0
From 8 to 17 weeks post partum:				
Average decrease for all patients	10	12.8	10	15.8
Average decrease for those showing decrease	7	20.8	9	19.2
Average increase for those showing increase	1	17.0	1	14.0
No change	2	0	..	0

became more marked after delivery and at eight weeks post partum; the hemoglobin was 9.2 Gm. (59 per cent of the normal content). The hemoglobin per kilogram was also extremely low. As a rule, the hemoglobin for each person seems to be a rather fixed quantity with variation between narrow limits. With one exception, the hemoglobin of all of these patients in a period of eight weeks varied less than 10 per cent.

In tables 11 and 12 are listed the changes in hemoglobin and hematocrit values calculated on the basis of total amount. The method used in calculating the total hemoglobin has been described in an earlier

paragraph. The total amount of erythrocytes (leukocytes and platelets are included, but form only a small part of the total) is determined either by multiplying the cells per hundred cubic centimeters by the blood volume in cubic centimeters, divided by 100, or by subtracting the plasma in cubic centimeters from the blood volume. All antepartum values are divided by the first one obtained and the quotient multiplied by 100; thus all data are converted to a common basis, and changes in different patients can then be compared. Postpartum values were converted similarly, but the determination at term was used as the divisor. In other words, the first antepartum determination is assumed to be 100 per cent, and subsequent ones are expressed in percentage of increase or decrease relative to it. Similarly, postpartum determinations are expressed in percentage of decrease or increase, relative to the determination at term, which is assumed to be 100 per cent. Ante partum the cell mass increases proportionally more than the hemoglobin, but post partum both decrease by approximately the same amount. The antepartum increases occur early and are of considerable magnitude by the end of the second trimester, but reach their maximum at term. The average increase in cells at term is 20 per cent, and in hemoglobin, 13 per cent. The increase in hemoglobin and in cell volume is less than the increase in blood and plasma volumes. Therefore, there is a decrease in both of the former, and the statement made by Williams [7] that the hemoglobin and cell volume are relatively, but not actually, diminished is confirmed.

Variations in hemoglobin, especially increases occurring within a period of one or two weeks, are difficult to explain. We do not believe that such a marked increase occurred, but we do believe that there is a measurable increase. The total figures are based on three separate determinations, each with an appreciable error; however, all determinations were made with the same conditions and by the same persons, and therefore the figures are significant.

Changes in volume of some of the abdominal organs will materially alter the blood volume. Barcroft [23] has demonstrated in the dog that the spleen shrinks markedly during pregnancy. This squeezing out of erythrocytes with a hematocrit value undoubtedly much higher than that of the blood would explain some of the rapid changes in the blood. Furthermore, the liver is also a reservoir for blood, and because of its size, changes in volume would affect the hematocrit and hemoglobin even more than changes in the spleen. Additional evidence of marked changes in hemoglobin is found in new-born babies in whom in the first week there is a reduction of the hemoglobin of from 20 to 30 per cent or more. This is demonstrated clinically by the varying degrees of icterus and decreases in hemoglobin.

23. Barcroft, J.: Am. J. M. Sc. **179**:1, 1930.

COMMENT

In the first article of this series we[17] advanced the theory that the increase in blood and plasma volumes is necessary in part to supply the increase in maternal tissue, but that the major portion is required to permit proper gaseous metabolism on the part of the fetus. In this contribution we have demonstrated that the cell volume and amount of hemoglobin per hundred cubic centimeters of blood are decreased, but that the total amount of each is increased. There is no decrease in the size of the erythrocytes. There is also a decrease in serum protein and total electrolyte per hundred cubic centimeters of serum. Thus, there is a decrease in all factors concerned in maintaining the viscosity of the blood, which, of course, is also lowered, thereby probably decreasing the amount of work done by the heart without interfering with cell metabolism. While we have no plethysmographic data to confirm our theory, we believe that, owing to the absolute increase in blood volume and total hemoglobin, the increase in cardiac output and the decrease in viscosity, the volume of blood per minute supplying an organ is normal. Considerable support is given to this belief by the evident "well-being" experienced by the pregnant woman. It is a well known fact that the metabolism becomes more efficient during pregnancy, that weight is gained and retained after delivery and that, as a rule, multiparity does not preclude longevity, all of which would be impossible if pregnancy were habitually accompanied by tissue anoxemia.

CONCLUSIONS

Previously reported hemoglobin, hematocrit and erythrocyte values in pregnancy are, in many instances, at variance with each other, and the results are inconclusive because, with but few exceptions, the determinations were made with methods and apparatus which were not standardized, and they were not made on the same women throughout pregnancy. They are of value only in that they indicate the direction of the change.

Determinations of these constituents and of the blood volume were made on various groups of women for the different periods of pregnancy. While the means show a decrease in each substance, reaching a minimum in the last ten weeks, calculation of the difference between the means demonstrates that the change is of no significance.

Similar studies in which the same women were followed throughout pregnancy and the puerperium indicate that the following changes occur in the blood:

1. There is a definite decrease in the hemoglobin per hundred cubic centimeters of blood. The maximum decrease, amounting to 15 per cent, is from the twenty-sixth to the thirty-fifth week. At two weeks post

partum the hemoglobin is 17 per cent, and at eight weeks it is 14 per cent, below normal.

2. There is a slight but definite decrease in the hemoglobin per kilogram during pregnancy, and a more marked one after delivery. Apparently there is an attempt during pregnancy to compensate for the increase in tissue by increasing the hemoglobin, but post partum the stimulus is gone and there is a lag in the production of hemoglobin.

3. The changes in the hematocrit value are similar to those in the hemoglobin content. The maximum decrease during pregnancy is 14 per cent. The recovery after delivery is more rapid, although at eight weeks post partum the hematocrit value is still below normal.

4. The changes in the erythrocytes are also similar, but the count is normal at three weeks post partum, thus demonstrating the ability of the hematopoietic tissue to produce red cells, but its inability to stock them with the normal amount of hemoglobin.

5. The total amount of hemoglobin shows an average increase of 13 per cent, but individual cases show a marked gain during pregnancy and a retention of much of the gain post partum.

6. The total cell volume shows an average increase of 20 per cent, which is even greater in many individual cases, and a retention of many of the cells post partum.

7. The increase in plasma volume is definitely greater than the increases in cell volume and hemoglobin. Therefore, these constituents show a relative decrease and an absolute increase.

8. Since the erythrocyte is only a vehicle for transporting hemoglobin and since cell counts in pregnancy are often misleading, more time and care should be devoted to hemoglobin determinations.

9. In pregnancy a hemoglobin content under 10 Gm. per hundred cubic centimeters of blood should be diagnostic of anemia.

10. The changes in blood volume, cell volume and hemoglobin are a part of the mechanism by which the body is able to take care of its own increase in tissue and the metabolism of the fetus, with the expenditure of the least amount of work.

OSTEITIS DEFORMANS

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Czerny,[1] in 1873, first used the term "osteitis deformans" to describe softening and deformity of the tibia and fibula in a young soldier. Paget,[2] however, was unaware of this when he published his classic description in 1877 and suggested the term "osteitis deformans" because of his belief in the inflammatory nature of the lesion. Since that time, Roberts and Cohen [3] stated, more than three hundred cases of the disease have been described. In view of the fact that within four years we have observed thirty-four cases, it would appear that the disease is much commoner than was hitherto supposed. The increasing use of roentgenography is probably the explanation.

The present investigation, originally commenced in 1926 as an effort to ascertain the frequency of neurologic changes in osteitis deformans, expanded into a more comprehensive clinical and biochemical investigation.

REPORT OF CASES

CASE 1.—*History.*—F. N., a woman, aged 57, had complained of vague pains in her legs for twenty years. Seventeen years before examination the left shinbone became prominent, and five years later both legs appeared to be bent, so that she had great difficulty in walking. For ten years she had been unable to walk, and she complained of vague aches like neuritis all over the body; these were worse in winter. For five years the head had been getting larger. During the last few months, her eyesight had become very poor, and straight lines appeared wavy in both the horizontal and the vertical direction. Six years before examination, hematemesis, thought to be due to gastric ulcer, occurred, and five years later, further hematemesis. Three children were alive and well. The patient showed a characteristic large head, with frontal bossing; marked kyphosis, lordosis and scoliosis; a diamond-shaped abdomen with a wide costal angle; exaggerated outward and forward bowing of the femora, tibiae and fibulae, which were bent to such an enormous extent as to cause crossing of the legs in scissor-like fashion;

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1. Czerny, V.: Wien. med. Wchnschr. **23**:896, 1873.
2. Paget, J.: Tr. Roy. Med.-Chir. Soc. **60**:37, 1877; **65**:225, 1882.
3. Roberts, R. E., and Cohen, M. J.: Proc. Roy. Soc. Med. **19**:13, 1926.

the humeri were bent forward and outward, and the ulnae were bent to give decubitus valgus. Examination of the cardiovascular system showed: blood pressure, 160 systolic and 80 diastolic; slight cardiac hypertrophy; the apex beat in the fifth space just external to the midclavicular line; an accentuated aortic second sound; systolic murmurs at the base of the heart and in the mitral area; slight thickening of the radial and brachial arteries, and tortuous temporal arteries. Crepitations were heard at the bases of both lungs. The liver was slightly enlarged. In the central nervous system no abnormalities were detected. Examination of the fundi revealed bilateral subretinal hemorrhages deep to the retinal vessels, macular hemorrhages in the nerve fibers, edema and pallor of the retina and vision of 6/60. Slight albuminuria was present. The Wassermann reaction was negative. No calcified vessels were seen on roentgenoscopic examination. The blood count showed: hemoglobin, 75 per cent; red cells, 4,350,000; leukocytes, 12,400; color index, 0.86; a differential cell count of 60 per cent neutrophils, 32 per cent small lymphocytes, 4.5 per cent eosinophils and 3.5 per cent large hyaline cells.

CASE 2.—*History.*—M. W., a woman, aged 44, during convalescence after removal of a multilocular ovarian cyst six years before examination, had a spontaneous pathologic fracture of the left femur on attempting to fasten her boot-lace. Roentgenography showed the fracture to be in the middle third of the femur, and the bone to be widened throughout its length, with much rarefaction and areas of compact bone. On failure to secure healing by splinting, the bone was plated; at operation it was found to be very soft. On clinical examination at that time no changes were observed in the other bones, but roentgenographic examination of the skull showed a porous thick vault with sagging of the posterior fossa. The roentgenologic diagnosis was osteitis deformans. For ten years the patient had had aching pains across the top of the head and down the back of the neck, occasionally in the frontal region and sometimes associated with vomiting. The headaches occurred every few days and lasted from a few minutes to a few hours. Speech was slow and sometimes difficult. For one year before the fracture the patient noticed creepy feelings in both legs when at rest, as though the muscles were twitching. She stated that she had to get up and work the legs about. For seven years she had had urgency of micturition, and during the past year also frequency, three times at night and six times during the day. For six and a half years, she had suffered from noises in the ears like rushing water. During the past year there had been increasing weakness and almost complete inability to walk. In the last three months diplopia had occurred. The past history was not significant. The patient had six children, aged 24, 22, 20, 15, 12 and 4. Examination revealed marked bulging of both temporofrontal regions of the skull, anterolateral bowing of both femora and anterior bowing of both humeri; the rest of the skeleton was normal. Examination of the central nervous system showed slightly irregular pupils; bilateral wasting of the lower part of the trapezius muscle on both sides, with some winging of the scapulae; moderate wasting of the left calf, and a Babinski plantar response on the right side. Examination of the cardiovascular system showed a blood pressure of 135 systolic and 80 diastolic. There were slight thickening and tortuosity of the radial and brachial arteries, with visible pulsation. No gross cardiac hypertrophy was present. The eyes showed blue sclerae, nystagmus to the left, diplopia on the left side and unsustained nystagmoid movements to the right. The visual fields were normal; the disks were pale, with indefinite edges, and there was no papilledema. Otosclerosis was present in both ears. Roentgenography showed osteitis deformans of the skull,

vertebrae and femora. The spine showed marked flattening and compression of the lumbar vertebrae; the humeri gave a roentgenographic picture more in keeping with osteitis fibrosa than with Paget's disease.

Case 3.—A. R., a man, aged 40, had noticed two years before examination the beginning of throbbing pain, which started in the occipital region and spread forward toward the ears. The pains were continuous but were worse at night. There was also a feeling of heaviness across the forehead. Eighteen months before examination he had three attacks of partial syncope in which he almost lost consciousness but did not fall down. Examination revealed marked forward and slight outward bending of both tibiae and outward and forward bending of both femora, with bowed legs. There were no obvious changes in the skull. Examination of the cardiovascular system showed: marked tortuosity, thickening and visible pulsation of the radial, brachial and temporal arteries, with Corrigan's pulse; capillary pulsation; the apex beat in the fifth space of the midclavicular line; an accentuated aortic second sound; a faint diastolic murmur to the left of the sternum, and a systolic murmur in the mitral area. The blood pressure was 180 systolic and 0 diastolic; aortic incompetence was probably present. There were crepitations at the base of the left lung. On examination the central nervous system showed: bilateral partial ptosis; Argyll Robertson pupils, with the right greater than the left; some cutaneous analgesia on the outer aspect of the upper part of the right arm and of the left forearm; some reduction in the sense of deep pain in the calf, and absence of the ankle jerk on the right side. The optic disks were pale. There was deafness of the right and left middle ear. Roentgenographic examination showed a cotton-wool appearance of the tibiae and fibulae, typical of Paget's disease. The Wassermann reaction was positive for the blood and the cerebrospinal fluid. The latter was macroscopically clear but contained 114 white cells per cubic centimeter, 90 per cent small lymphocytes and 0.03 per cent protein. Meningovascular syphilis was undoubtedly present in this case, but roentgenographic examination and estimation of the phosphatase content of the blood plasma indicated coexisting osteitis deformans.

Case 4.—C. G., a man, aged 62, sustained a fracture of the neck of the left femur eight years before examination, following a severe fall. Union had taken place with external splinting. Eighteen months before examination, fracture of the neck of the right femur occurred following a fall. Examination revealed the following: marked forward and outward curving of both femora, especially the right, with bowing of the legs and separation of the internal condyles by 3 inches (7.6 cm.); gross thickening of the left clavicle, and a diamond-shaped abdomen with a wide costal angle. There were no obvious changes in the skull or spine. The findings on examination of the cardiovascular system were marked thickening and tortuosity of the brachial arteries, with visible pulsation, the tortuosity being excessive and snakelike. The radial arteries were apparently not affected. The blood pressure was 140 systolic and 90 diastolic; the apex beat occurred in the fifth space of the midclavicular line. Auricular fibrillation was present. No changes were found on examination of the central nervous system. There was gross pyorrhea. Roentgenographic examination of the left femur and pelvis showed osteitis deformans.

Case 5.—W. L., a man, aged 50, had noticed that his vision was beginning to fail eighteen years before examination. Objects appeared dim, and reading became difficult. For twelve years this state of vision remained unchanged. Fourteen years before examination transitory paresis of both legs occurred. For ten years

there had been indefinite mental trouble, with several attempts at homicide and attacks of loss of memory. Shortly before examination he noticed deafness in the right ear and giddiness on rapid change of position. For five years he had had attacks of diplopia. He was addicted to alcohol. In 1910 the patient was seen by Foster Moore, who reported partial optic atrophy caused by anemia resulting from bleeding piles. The patient had suffered from the latter condition for ten years. The blood count at that time showed 40 per cent hemoglobin and 3,900,000 red cells. On Aug. 17, 1910, the piles were ligated. On October 27 the hemoglobin was said to be 100 per cent. The eyes were examined in 1918, and no appreciable change was observed. Examination revealed no gross changes in the skull or in any of the skeletal structures. Examination of the central nervous system showed that the pupils were equal but irregular, with poor reaction to light; they reacted well on convergence. The ocular movements were full, and there was no ptosis, squint or nystagmus. A slight relative nasal analgesia was evident; the facial movements were good and equal. The tongue protruded in the midline, and the palate moved symmetrically on phonation. There was no weakness, ataxia, wasting or dystonia. Hearing was diminished in both ears. The reflexes of the arm were normal. The abdominal reflexes were present and were equal; the knee jerks were present, although they were slightly diminished. The ankle jerks were obtained with difficulty. The plantar reflexes and postural sensibility were normal. There was relative thoracic analgesia from the second to the sixth dorsal segment. Examination of the cardiovascular system showed a blood pressure of 210 systolic and 110 diastolic. The radial and brachial arteries were thickened and slightly tortuous; no cardiac hypertrophy was detected. On examination of the eyes, fingers were seen at 1 foot (30.5 cm.) by the right eye and at 2 feet (61.2 cm.) by the left; the media were clear in both eyes. Both disks were pale, with cleancut edges; the physiologic cup showed the lamina cribrosa. There was no retinitis and no exudate along the vessels. Bilateral primary optic atrophy was found. The visual fields were not contracted. Irregular central scotoma was found in both fields. On roentgenographic examination no enlargement of the pituitary fossa was apparent; the clinoid processes could be plainly seen. There was no erosion, and the general view of the skull strongly suggested Paget's disease: the skull was thick; in places there was loss of differentiation between the inner and outer tables (thickened diploe); the bones were bottled, suggesting areas of thickening and rarefaction side by side. No abnormalities were seen in the tibiae. Dr. Vilvandré expressed the opinion that the changes in the skull were characteristic of Paget's disease. The Wassermann reaction was negative for the blood and the cerebrospinal fluid. Spinal puncture yielded 6 cc. of clear, colorless fluid in which no cells were found. The normal protein was 0.17. The urine was normal. A blood count showed: red cells, 4,500,000; hemoglobin, 75 per cent; color index, 0.83, and leukocytes, 7,800.

Case 6.—A. L. B., a woman, aged 49, had suffered for seven years from lumbago, and for six years from pains in the knees, elbows and shoulders. For three years she had been unable to walk and was bedridden. Two years before examination the small joints of the hands were affected, becoming stiff and swollen. For seven years she had had amenorrhea, and two years before examination her teeth were extracted because of pyorrhea. She was married and had four children, the youngest of whom was 21 years of age. Examination revealed partial fixation of all the joints, with limited painful movements; glossy skin; ulnar deviation of the hands; lordosis, scoliosis and fixity of the spine. There was a slight outward bending of the femora. The costal angle was wide. No obvious changes

were found in the skull. Examination of the cardiovascular system showed a blood pressure of 210 systolic and 120 diastolic; the arteries were not grossly thickened. The apex beat was not located; there was a systolic murmur in the mitral area. The central nervous system was apparently normal. Roentgenography showed changes in both femora suggestive of osteitis deformans. Although the clinical picture suggested the diagnosis of rheumatoid arthritis, the roentgenograms and the high phosphatase content of the blood plasma indicated coexisting osteitis deformans.

CASE 7.—S. B., a woman, aged 68, had suffered from vague malaise for many years. She gave an indefinite history of paresis of the right arm several years before examination, followed by gradual recovery. Six weeks before examination, pain occurred in the left foot, with bluish discoloration, and there was some frequency of urination. Examination showed a thin old woman with marked bulging of the right parietal bone and enlargement of the head, the enlargement being limited, however, to the right side. The right femur was markedly bent in an outward direction, and the right tibia was bent forward and outward. The right ulna had a marked convexity in an outward direction, the arm being held in the pronate position. In contrast, the left arm and leg were apparently normal. The abdomen was diamond-shaped, with a wide subcostal angle. Examination of the cardiovascular system revealed a blood pressure of 200 systolic and 100 diastolic but with pulsations faintly heard down to 0. The blood pressure of the leg below the knee was 280 systolic and 160 diastolic. Cardiac hypertrophy was present. The apex beat occurred 1 inch (2.54 cm.) external to the midclavicular line; accentuated aortic second sounds with systolic murmurs were located at the base of the heart and in the mitral area. No aortic diastolic murmur was heard at the time of examination. All the vessels of the right leg were patent. On the left side the popliteal artery pulsated, but the posterior tibial artery and the dorsalis pedis were closed. Oscillometry showed absence of pulsation at the left ankle. The brachial and radial arteries were thick and tortuous, with visible pulsation and a collapsing pulse; the temporal arteries were thickened and tortuous. Roentgenography showed changes of osteitis deformans in the right femur. (In this case, as in several other cases, roentgenographic examination was limited to one or two bones for economic and other reasons.) The Wassermann reaction was negative. A few months after the patient was seen, sarcoma of the right femur developed.

CASE 8.—A. S., a woman, aged 49, had symptoms which had begun with pains in the head and right leg ten years previous to examination. The headache was of dull character and was especially noticeable in the right temporal region. For three years the patient had been getting deaf. During the last few years there had been dull, aching pains in the arms and legs. One year the right foot had twitched involuntarily. The patient had felt sleepy, and the lid of the right eye had tended to droop. During this period the head had been increasing in size. For six months there had been pain in the right shoulder as though a needle was being thrust there. There had also been some incontinence of urine and frequency of micturition. Examination showed gross enlargement of the skull, which was of enormous breadth, and marked bulging of the temporal and frontal regions, with apparently sunken orbital fossas. There were slight scoliosis and slight thickening of the upper end of the left tibia. Otherwise, there were no gross skeletal changes. On examination of the cardiovascular system the fundi showed arteriosclerosis of the retinal vessels. The blood pressure was 180 systolic and 100 diastolic. There were slight cardiac hypertrophy, the apex beat being in the fifth space of

the midclavicular line, an accentuated aortic second sound, and some thickening of the radial and brachial arteries, with marked tortuosity and thickening of both temporal arteries. No abnormalities were found in the lungs. There was deafness of the right middle ear. In the central nervous system all the reflexes were increased in the lower limbs, but the plantar reflex was normal. Roentgenography revealed osteitis deformans. The Wassermann reaction was negative.

CASE 9.—R. T., a woman, aged 54, had a history of aching pains in the legs, thighs and right arm of eleven years' duration. The legs gradually became bent, and five years before examination tended to cross one another in walking. The patient began to stoop and experienced some pain in the lumbosacral region. Three years before examination the pain spread upward and involved the whole spine and the back of the head. The pain was much worse when the patient stood still; she was unable to maintain an erect position for more than a few minutes, but was, nevertheless, able to walk. The head was becoming larger, and there was a dull ache in the left parietal region, which was usually likened to a nagging toothache, with acute exacerbations. There was some pain in the left foot. The patient was examined in 1925. The records stated that she had a broad, square forehead, thickening and outward bowing of the right humerus, anterolateral bowing of both femora and thickening and slight curving of both tibiae, which was greater on the right than on the left. No gross abnormalities of the spine were found, but there was a slight decrease in the lumbar curvature. At that time Robert Milne performed an osteotomy on the right femur. Microscopic examination showed osteitis deformans of the cortex of the femur. The bone was composed of numerous lamellar systems and was permeated by medullary spaces and widened haversian canals; these were occupied by delicate fibrous marrow. Toward one surface there was active resorption and deposition. The Wassermann reaction was negative. Examination disclosed: a very broad head with protuberant supra-orbital ridges, which were greater on the right than on the left; definite enlargement of both clavicles, which was more pronounced on the right than on the left; marked lordosis and kyphosis; a wide costal angle with a sulcus on the wall of the chest, and marked bowing of both femora and both tibiae. Examination of the cardiovascular system revealed a blood pressure of 165 systolic and 80 diastolic. Gross cardiac hypertrophy was found. There was accentuation of the aortic second sound; the apex beat occurred in the fifth space, ¾ inch (1.9 cm.) external to the midclavicular line. Marked thickening and tortuosities and visible pulsation of the radial, brachial and temporal arteries were present. The lungs and the central nervous system were normal.

CASE 10.—H. A., a man, aged 60, had noted bending of the left tibia for thirty years, and bending of the right tibia for almost as long. A few months after the onset of this trouble his head had begun to grow larger, so that while he had formerly worn a size 6⅞ hat, he gradually came to need a 7¾. Practically coincident with the change in the shape of the leg he noticed shooting pains of knifelike character up and down the long axis of the leg. These occurred in attacks at intervals of a few weeks. They lasted only a few minutes but left a sensation of soreness which persisted for several hours or longer. If the pains came on while the patient was walking they were sufficiently severe to force him to stop, but they did not have the character of claudication. There was, however, no pain in the head until three years before the patient was examined, when shooting pains began in the temporal or occipital region, lasting a variable time. At first they occurred every few weeks, but at the time of examination they occurred every day and several times a day. Owing to progressive bending of

the lower limbs, the patient had been unable to walk for ten years. For many years he had suffered from chronic bronchitis. Examination showed a skull characteristic of Paget's disease, with marked bulging of the frontal, parietal and occipital bones, and bowing of both humeri, which was greater on the left than on the right, with decubitus valgus. The clavicles were thick and prominent; the costal angle was wide, and splaying of the ribs, gross kyphosis and lordosis were apparent. There was enormous forward and outward bowing of the femora and tibiae, that of the tibiae being so excessive that the legs were crossed in scissor fashion. Examination of the cardiovascular system showed marked thickening and tortuosity of the radial, brachial and temporal arteries. The blood pressure, however, was not high (135 systolic and 76 diastolic), and there was no gross cardiac hypertrophy. Scattered rhonchi could be heard throughout the lungs. There were no changes in the central nervous system. The Wassermann reaction was negative. The fundi showed choroiditis with secondary optic atrophy (Jeremy).

Case 11.—E. L., a woman, aged 70, had suffered from delusional insanity while in the infirmary, where she was examined by one of us. It was impossible to obtain any definite history from the relatives. On examination the head was found to show the characteristic changes of Paget's disease; there was marked bulging of the right frontal and occipital regions. The clavicles were slightly enlarged, and there was well marked kyphosis. The costal angle was not widened, and no gross changes were observed in any of the limbs except some outward and forward bending of the left tibia. Marked cardiovascular hypertrophy, with thickening of the radial and brachial arteries and tortuosity of the temporal vessels, was apparent. The blood pressure was 160 systolic and 80 diastolic; the apex beat was in the fifth space ½ inch (1.27 cm.) external to the midclavicular line; accentuation of the aortic second sound was detected. During examination of the central nervous system the patient gave no evidence of any delusions which the sister in charge stated had occurred at varying periods. However, she exhibited a very sluggish mentality, and it was practically impossible to obtain any response to questions. The pupils were irregular, the left being slightly greater than the right. Reaction to light and in accommodation was present. There was some keratitis of the right eye, with diffuse corneal opacity. The fundi, however, appeared to be normal. All the reflexes were elicited and were equal on both sides. There appeared to be loss of postural sensibility and vibratory sense in the left leg, and incomplete loss on the right. On roentgenographic examination the left tibia and the skull showed changes typical of osteitis deformans. Roentgenographs of the femora and of the right tibia, radius and ulna showed no abnormalities. The Wassermann reaction was positive.

Case 12.—S. G., a woman, aged 65, had been confined to the infirmary for six years. Four years before examination she fractured her left femur; since that time she had been confined to bed. She complained of very severe headache but was unable to describe it. During the six months before examination she had three attacks of convulsions, with loss of consciousness. These were not accompanied by incontinence of urine or biting of the tongue. There was generalized twitching during the attacks but no evidence of focal spread. During the last attack she had repeated convulsions (status epilepticus); the attack had lasted four hours and had been followed by a comatose state of forty-eight hours' duration. Examination showed gross enlargement of the skull characteristic of osteitis deformans, with marked bulging of both the temporal and the frontal regions. The clavicles were grossly thickened. No obvious change was found in the upper limbs except definite tenderness at the lower end of the right humerus (spon-

taneous fracture?). The costal angle was very obtuse, with outward splaying of the ribs. The abdomen was diamond-shaped, and the pelvis was wide. There were moderate kyphosis, gross outward bending of the femora and forward and outward bending of the tibiae, the internal condyles of the femora being separated by 5 inches (12.7 cm.) when the internal malleoli were in contact. Examination of the central nervous system showed monoplegia of the left arm, with rigidity, increased reflexes and some general wasting. The left leg gave no evidence of paralysis except for a slight increase of the reflexes, as compared with the right leg. The plantar responses were normal; the abdominal reflexes were not obtained. The pupils were equal and regular. Accommodation and reaction to light were sluggish. Examination of the fundi revealed a small hemorrhage below and external to the left disk. Bilateral deafness of the middle ear was present. Examination of the cardiovascular system revealed thickening and tortuosity of the radial, brachial and temporal arteries, with visible pulsation. The systolic blood pressure was 120; the diastolic was indeterminate, pulsations being heard over the whole range down to zero. There was some cardiac hypertrophy. The apex beat was in the fifth space of the midclavicular line. A systolic murmur was audible at the base and apex of the heart. No thrill was present. Accentuation and roughening of the second aortic sound were found, but no diastolic murmur was heard. The pulse tended to be dicrotic, and aortic incompetence was suspected. Crepitations were heard at the bases of both lungs.

Case 13.—E. R., a woman, aged 39, had experienced a vague aching over the whole back for two years. This had become increasingly more severe. The pain often started in the right lumbar region and gradually spread upward toward the shoulders, but during the last few months before examination it had been more severe on the left side. The pain was described as hot, gnawing and continuous, with periodic stabbing exacerbations. It was aggravated by exertion or by the carrying of heavy objects and was relieved when the patient lay down. A similar type of pain occurred in the knees and shins and, later, in the joints of the elbows. For eighteen months before examination the patient had felt that she was stooping and that her shoulders were becoming rounded. About a year before examination a masseuse at a Turkish bath noticed that the spine was bent. For twelve months the head had been growing larger, and the patient had to buy larger hats. For one year the eyesight for near objects had gradually deteriorated. Shortly before examination the pains in the back and limbs had become sufficiently severe to disturb the patient's sleep. Examination showed gross changes in the skull characteristic of Paget's disease; bulging of the temporal bones; a prominent occiput, with some enlargement of the vertex of the skull; marked prominence of both clavicles, with thickening and exaggeration of the anterior convexity, and slight thickening of the left humerus. The femora were apparently unchanged. There were a slight anterior convexity of the right tibia and marked kyphosis and some scoliosis, with apparent prominence of the ribs on the right side posteriorly. The costal angle was not increased. Examination of the cardiovascular system showed a blood pressure of 120 systolic and 70 diastolic. There was no evidence of any changes in the arteries; no cardiac hypertrophy was present, and the heart sounds were normal. No abnormalities of the central nervous system were found. Roentgenography confirmed the diagnosis of osteitis deformans.

Case 14.—W. H., a man, aged 41, had pains in the lower limbs and the back for six years. These were aching in character and were worse when the patient walked. The pains in the legs were often acute, even at rest, and occurred in attacks lasting about half an hour at intervals of a few days. For five years the

patient had noticed bowing of the legs. A short time before he was examined he complained of general weakness. Examination showed some enlargement of the skull, with prominence of the frontal and parietal regions; moderate scoliosis, kyphosis and lordosis; thickened and prominent clavicles; a diamond-shaped abdomen with a wide costal angle; slight outward bending of the left radius, and gross outward and forward bowing of both femora and both tibiae, with bowing of the legs. Marked cardiovascular hypertrophy was present. The blood pressure was 160 systolic and 110 diastolic. The apex beat was in the sixth space, ½ inch (1.27 cm.) external to the midclavicular line. Accentuation of the aortic second sound and thickening and tortuosity of the radial, brachial and temporal arteries were found. Examination of the central nervous system showed that the reflexes of the lower limbs were brisk; they were greater on the left than on the right. The plantar reflex was normal on the right but was not obtained on the left. On roentgenographic examination the skull showed the typical nigger-hair appearance of osteitis deformans, and the pelvis was typically dense, woolly, patchy and thickened. The appearance of the femora was typical: the cortex was bent and thickened, with areas of translucence, and the pattern and texture were accentuated. Typical changes were found in the tibia. The spine showed the typical dense and woolly appearance (Jupe). The Wassermann reactions was doubtfully positive.

Case 15.—E. M., a man, aged 60, was admitted to the hospital because of a condition diagnosed as resolving appendicitis. It was noticed that the head was enlarged in a manner suggestive of osteitis deformans, and the patient stated that during the last eight years he had required progressively larger hats. The size which he was wearing at that time was 7½, as contrasted with the original 6⅞. For several years he had suffered from increasing deafness on the left side. Examination showed an enlarged skull, with bulging of the frontal and occipital regions, and a long ridge on the vertex; gross forward and outward bowing of the femora; saber-shaped tibiae; some bending of the humeri and radii, and a diamond-shaped abdomen with a wide costal angle. Examination of the cardiovascular system showed thickening of the radial and brachial arteries, with visible pulsation. The pulse was not markedly collapsing. The systolic blood pressure was 150, the diastolic, 0, the pulsation being heard right down to 0. The apex beat was not located. There was a systolic murmur in the mitral area; the sounds at the base of the heart were distant, and no diastolic murmur could be detected. The high pulse pressure suggested aortic incompetence. The central nervous system showed no abnormalities. The fundi were normal except for arteriosclerosis of the retinal vessels. There was deafness of the left middle ear. Roentgenography showed changes characteristic of osteitis deformans. The Wassermann reaction was negative.

Case 16.—L. B., a woman, aged 60, had noticed bowing of the legs and vague, generalized pains for four years. Examination showed no gross changes in the head, although there was some bulging in the temporal region. Curvature of the ulnae was found, which was greater on the right than on the left, with decubitus valgus. Other findings were: marked outward and forward bowing of the femora, with genu varum; forward bending of the tibiae; gross enlargement of both clavicles, especially the right; a diamond-shaped abdomen with a wide costal angle and a broad pelvis, and bilateral arthritis of the knees, with some wasting and atonia. Examination of the cardiovascular system showed thick and tortuous radial, brachial and temporal arteries, a blood pressure of 120 systolic and 100 diastolic and some cardiac hypertrophy, with accentuation of the aortic second

sound. Examination of the central nervous system revealed slight convergent strabismus; otherwise no abnormalities were found. There was bilateral deafness of the middle ear. Roentgenography showed osteitis deformans.

CASE 17.—L. P., a woman, aged 55, stated that she had been bow-legged for many years, but not as a child. She was admitted to the hospital with a fracture of the middle third of the left femur, which had been caused by a fall from a chair. Examination showed that the skull was not obviously affected. There was gross outward and forward bowing of both femora, with genu valgum. Examination of the cardiovascular system showed gross thickening and tortuosity of the radial, brachial and temporal arteries, a blood pressure of 200 systolic and 110 diastolic, the apex beat in the fifth space ½ inch (1.27 cm.) external to the midclavicular line and an increased aortic second sound. The central nervous system showed no abnormalities. The Wassermann reaction was negative.

CASE 18.—S. B., a woman, aged 50, had suffered for seven years from aching and shooting pains in the right leg, chiefly on the inner side of the tibia above the ankle. The pain was worse when she walked. During the last few years the pain had spread upward to the hip and the lumbar region. In 1925 the right tibia was found to be bent forward and greatly thickened anteriorly. There was tenderness of the bone and of the muscles of the calf. Linear osteotomy was performed by Sir Hugh Rigby and microscopic examination of the removed piece of bone showed changes typical of osteitis deformans. During the last few years before examination there had been some frequency of micturition, two times during the night and six times during the day; there was some difficulty and pain in beginning. Examination showed no obvious enlargement of the skull but revealed outward and forward bowing of both femora and anterior bending of the right tibia; well marked scoliosis, kyphosis and lordosis, with rigidity in the lumbar region; well marked thoracic sulcus with a wide costal angle; a diamond-shaped abdomen, and a broad pelvis. On examination of the cardiovascular system no gross changes were found in the arteries; the blood pressure was 130 systolic and 80 diastolic. In the central nervous system the optic disks, the pupils and the cranial nerves were found to be normal. There was no weakness, ataxia, dystonia or wasting of the upper limbs. The reflexes in the upper limbs were brisk and equal. There were diminished appreciation of pinprick, cotton-wool and heat on the left arm and some general weakness of the lower limbs, without wasting, ataxia or dystonia. The reflexes were brisk and equal, and there were diminished sensation to pinprick over the right leg and the outer side of the left leg and indefinite and patchy anesthesia and analgesia, which gradually became less defective on ascending toward the thigh. On both legs there was a marked defect in appreciating warmth; the defect continued onto the trunk, there being slight relative cutaneous anesthesia and analgesia up to the fifth thoracic level. The Wassermann reaction was negative. Roentgenograms of the skull and femora showed the characteristic changes of osteitis deformans.

CASE 19.—E. R., a man, aged 52, had had pains in all his joints, especially in those of the left hip, for several years. The pains were aching in character and occurred every day. At night he had noticed cramps in both legs, as if the muscles were being pulled apart. There was an increasing tendency to stoop, and the effort to stand erect was associated with much pain. There were also troublesome headaches, particularly in the occipital and temporal regions, and the head had gradually increased in size, requiring a 7⅞ size hat, whereas the patient had formerly worn a 6⅞ size. Increasing deafness had occurred during the year pre-

ceding examination. Examination showed a grossly enlarged head with marked prominence in the temporal and supra-orbital regions. Both femora were bowed outward and forward, and genu varum was present. The tibiae were not obviously affected; the clavicles were thickened; the spine showed marked kyphosis. Examination of the cardiovascular system showed gross thickening and tortuosity, with visible pulsation of the radial, brachial and temporal arteries, and marked cardiovascular hypertrophy, the apex beat being 1 inch (2.54 cm.) external to the midclavicular line. The blood pressure, however, was only 140 systolic and 60 diastolic. The central nervous system showed no abnormalities. There was bilateral otitis media. The Wassermann reaction was negative. Roentgenography gave positive findings.

CASE 20.—J. B., a man, aged 71, had had pains in the left thigh and knee for six years and had been unable to tolerate any pressure on the left knee. For two years there had been marked wasting and limitation of movement in the region of the left hip. For one year there had been slight headaches in the right temporal and retro-ocular regions and diplopia on looking to the left; apparently the latter feature was not constant. The head had been growing larger during the eight months preceding examination. More recently some deafness had been observed on the left side. The patient thought that there had been a tendency to bowlegs within the last few years; this had been more marked on the left side. Examination showed no gross changes in the skull. Movement of the left hip was limited in all directions. Other findings were: forward and outward bowing of both femora, with genu varum and separation of the internal condyles by 3 inches; a wide costal angle; a diamond-shaped abdomen, and a broad pelvis. Examination of the cardiovascular system showed moderate thickening and tortuosity of the radial, brachial and temporal arteries; a blood pressure of 160 systolic and 85 diastolic; slight cardiac hypertrophy, and bradycardia, with a pulse rate of 54. Examination of the central nervous system showed normal disks and pupils, diplopia on looking to the left and nystagmoid movements on extreme deviation to the right or left. The other cranial nerves were normal. The upper limbs showed no abnormalities. There was relative analgesia of the left leg over the third and fourth lumbar segments. The Wassermann reaction was negative. Roentgenography revealed thickening of the outer plate of the skull, with sclerosis. Atheromatous arteries could be seen. The changes in the skull were not more characteristic of Paget's disease than of syphilis. The changes in the bones of the pelvis and left tibia, however, were typical of osteitis deformans. There was osteo-arthritis of the left hip.

CASE 21.—F. G., a woman, aged 55, had experienced stabbing pains in both legs for five years. The pains traveled along the long axis of the limbs from the knee downward. They occurred several times a day and were of momentary duration. They sometimes caused the legs to give way and the patient to fall. Occasionally they lasted for several hours and were then of burning character, leaving a persistent soreness over the skin of the shin-bone. There were occasional vague pains in the upper part of the left arm. The patient also suffered from severe headaches during this period; these were throbbing in character and occurred over the right eye and in the occipital region; they were fairly constant. During the same period there had been gradual forward bending of the tibiae, the changes in the right tibia having begun one year before those in the left. For two years there had been frequency of micturition (two times at night and twelve times during the day), and failing vision. The menopause had occurred six years before examination. The patient had been treated for three years with suprarenal extract

in doses of 5 grains (0.32 Gm.) three times a day, with almost complete disappearance of pain. Examination showed no gross changes in the skull. There were forward and outward bowing of the femora and anterior bending of both tibiae, with genu varum; marked lordosis and kyphosis, with lumbar fixation, and some bending of the forearms, especially of the radii, which was greater on the left than on the right. Examination of the cardiovascular system revealed moderate thickening of the arteries, with cardiac hypertrophy. The apex beat was in the fifth space just external to the midclavicular line, and the blood pressure was 185 systolic and 110 diastolic. There was a tendency to myxedema. The central nervous system was normal.

CASE 22.—E. T., a woman, aged 53, had had symptoms consisting of pain in the left shoulder and forearms for several years. The pain was aching in character; it occurred only occasionally. The patient came under observation because of an inquiry into the family history of her brother, who was in the hospital (case 23). Examination showed no gross changes in the head, but there was some slight bulging of the occiput. The clavicles were enlarged and prominent; the left radius had a marked outward convexity and appeared to be somewhat elongated; the costal angle was not wide; the femora were bowed in an outward and forward direction, the condyles being separated by 2 inches (5.08 cm.); there were no gross changes in the tibiae. Examination of the cardiovascular system showed only a slight thickening of the arteries; the blood pressure was 120 systolic and 80 diastolic, and there was some accentuation of the aortic second sound. On roentgen examination the skull appeared to be rarefied, but unevenly so, so that a large parietal island of denser bone remained surrounded by some smaller dense areas; the differentiation between the inner and outer tables was well seen. The left femur was thickened in the upper two thirds, and osteitis was present. There was a lack of differentiation between the medulla and the compact layers. The right femur was similar to the left; there was a marked patch of rarefaction in the upper end about the greater trochanter. The left radius was elongated, thickened and apparently twisted, being overlong for its allotted space; the lower half was somewhat thinner and less dense, giving an appearance suggestive of osteitis fibrosa.

CASE 23.—G. L., a man, aged 49, had noticed gradual bending of the right forearm for ten years, the right wrist having become prominent. For eight years there had been a gradual increase in the size of the head; at the time of examination the patient wore hats size 7½; formerly he had worn size 6⅞. For one year there had been aching in the right leg after standing for a long while. The patient was admitted to the hospital complaining of severe pains in the right leg and thigh of one month's duration. The pains woke him at night and prevented much walking. The condition was found to be due to a pathologic fracture of the neck of the femur, of which there was no definite history but which was revealed by roentgen examination. The fracture was incomplete and not unlike a greenstick fracture; there was no displacement. Examination showed gross enlargement of the skull, with frontal bossing, which was greater on the right than on the left; sunken orbital fossae, and pronounced occipital protuberance. Both clavicles were enlarged. The right forearm was grossly distorted, the radius having a marked outward and dorsal convexity and the styloid processes of the ulna being especially prominent. The left arm appeared normal. There were marked kyphosis and lordosis, with slight scoliosis and prominence of the left scapula. The costal angle was wide, and the abdomen was diamond-shaped. The femora were bowed in a forward and outward direction, with genu varum and

separation of the inner condyle by 2¾ inches (6.9 cm.). The tibiae were not grossly involved. There was some creaking of the right knee. Examination of the cardiovascular system revealed: moderate thickening of the brachial arteries, a blood pressure of 145 systolic and 90 diastolic, the apex beat in the fifth space of the midclavicular line and some accentuation of the aortic second sound. The Wassermann reaction was negative. On roentgen examination the changes in the skull, femur and pelvis were found to be characteristic of Paget's disease, but the condition of the radius, as in case 22, bore some resemblance to osteitis fibrosa.

Special Note: This patient and the patient in case 22 were brother and sister, and therefore the cases are of interest in demonstrating a possible family incidence of osteitis deformans. It was also ascertained that curvature of the spine developed in the mother in middle age and that she had to wear a spinal jacket. She died at the age of 65, and, although it was impossible to obtain any further information, it seems not unreasonable to suspect that her condition was Paget's disease. Another interesting feature was the unilateral involvement of the radii in this and in the previous case, the left radius being involved in the left-handed patient and the right in the right-handed patient, thus apparently illustrating the effect of function on the development of curvature of diseased bones.

Case 24.—M. L., a woman, aged 78, had noticed prominence of the left knee and pains in both legs for four years. The latter occurred mostly at night along the long axis of the limbs from heel to knee and were of a shooting character. The legs gradually became bent, and people observed that the patient's head was getting larger. For three years she had suffered from severe headaches of the vertex, which were "maddening" in character, like the pressure of a weight or the trickling of water. For two years she had frequency of micturition and urgency of defecation. She was able to walk quite well with the aid of a stick. Examination showed no gross changes in the skull but a slight bulging of the right frontal region. Some enlargement of the clavicles, slight decubitus valgus and a wide costal angle were found. There was marked forward bowing of the left tibia, but the right tibia was normal. There was also marked outward and forward bowing of the right femur and, to less extent, of the left. The spine showed no gross changes. Examination of the cardiovascular system showed: thickening and tortuosity, with visible pulsation of the brachial, radial and temporal vessels; the apex beat 1 inch (2.54 cm.) external to the midclavicular line and in the fifth space; accentuation of the second sound in the aortic area; a diastolic murmur to the left of the sternum; a systolic murmur in the pulmonary and mitral areas; a collapsing pulse; a blood pressure of 200 systolic and 40 diastolic, and aortic incompetence. Examination of the lungs showed scattered rhonchi. The central nervous system was normal. Roentgenography revealed marked changes in the tibiae and femora typical of osteitis deformans, with slight changes in the skull.

Case 25.—J. B., a man, aged 50, had a pathologic fracture of the right tibia six years before examination. Since that time, he had had pains in the legs and forearms; these were gnawing in character and were eased by suprarenal extract. In addition he experienced dull, continuous, frontal headaches. For the three years preceding examination he had noted increasing prominence of his forehead. He was admitted to the hospital with a pathologic fracture in the proximal third of the femur, just distal to the lesser trochanter. For three years he had some frequency of micturition, two times at night and five times during the day. The skull showed bulging of both temporofrontal regions and marked supra-orbital ridges. Both clavicles were thickened. A wide costal angle and a diamond-shaped

abdomen were found. There was slight outward curving of both femora, with bowlegs and saber-shaped tibiae. The lower end of both ulnae was prominent, especially that of the left, which was painful. Examination of the cardiovascular system revealed slight thickening of the arteries and tortuous temporal arteries. The apex beat was in the sixth space, ½ inch (1.27 cm.) external to the midclavicular line. There was a systolic murmur in the mitral area. The blood pressure was 120 systolic and 80 diastolic. The central nervous system showed no abnormalities. Deafness of the right middle ear was present. The Wassermann reaction was positive. Roentgenography showed changes in the femur, tibia and skull characteristic of osteitis deformans, the skull being only slightly affected.

CASE 26.—M. H., a woman, aged 54, fell on her knee in 1924, and traumatic synovitis developed. Roentgen examination of the knee suggested osteitis deformans. Since that time the patient had had recurrent arthritis of the joint of the left knee. In 1927 further roentgenographs of the femora and tibiae showed typical osteitis deformans. Great relief of pain followed the administration of suprarenal extract. For several years a stoop had gradually developed, and a friend suggested that the patient was becoming bandy-legged. No gross changes in the skull were found on examination. Kyphosis, lordosis and decubitus valgus were present, without marked curvature of the radii. There were gross forward and outward bending of both femora and forward bending of the right tibia, with separation of the internal condyle by 2 inches (5.08 cm.) and creaking of the right knee. Examination of the cardiovascular system showed no gross thickening of the arteries. The pulse was not collapsing. The systolic blood pressure was 125, the diastolic, 0, the pulsations being heard down to 0. No diastolic murmur was heard in the aortic area or over the precordium. The aortic second sound was accentuated, but the apex beat was not displaced. Examination of the central nervous system gave negative findings. Roentgen examination of the femora and tibiae showed changes typical of Paget's disease. The skull was not affected.

CASE 27.—L. I., a woman, aged 63, had experienced pains in the legs, and to a less extent in the arms, for three years. These were throbbing and continuous and were worse at night and on exertion. There had been a marked increase in the size of the head, with prominence of the orbital and occipital regions, and the legs had become bowed. The patient had experienced dull, continuous frontal headaches, with throbbing of the temporal arteries, and formication over the head at night. There had also been cramps of the legs at night and occasional nocturnal frequency. Examination revealed: gross enlargement of the skull; bowing of both bones of the forearms, especially the ulnae; gross enlargement of both clavicles; marked forward and outward bowing of both femora, and anterior bending of both tibiae, with genu varum. Examination of the cardiovascular system showed thickening of the arteries, with visible brachial and temporal pulsation. The blood pressure was 110 systolic and 40 diastolic. At the pressure of 40 the pulsations became less loud but were continued down to 0. The apex beat was located in the fifth space of the midclavicular line. The aortic second sound had a slapping and prolonged character, but there was no diastolic murmur. On examination of the central nervous system the disks, pupils and cranial nerves appeared normal. The upper limbs were normal. Anesthesia and relative analgesia to cotton-wool and pinprick were present in both lower limbs and in the trunk, gradually decreasing up to about the second

dorsal vertebra. There was a similar deficiency in the appreciation of heat and cold. The vibratory sense and postural sensibility were normal. The knee jerks were present and were equal; the ankle jerks were sluggish; the plantar reflex was normal. Roentgenography showed generalized osteitis deformans.

CASE 28.—E. B., a man, aged 69, was admitted to the hospital for prostatectomy. Examination showed some forward bending of the right tibia, and when the patient was examined with the possibility of osteitis deformans in view several changes were observed. Questions elicited the facts that the patient had always worn large-sized hats (7¼) but that during the last fifteen years there had been an increase in the size of the skull; he was wearing hats size 7⅜ at the time of examination. His grandsons, aged 8½ and 8 years, both required size 7 hats, but their skulls showed no abnormality on roentgenographic examination. The patient's back had gradually become bent during many years, but this had been attributed to his occupation of ship repairer. Three years before examination he had severe hematemesis and melena, preceded by dyspeptic symptoms which were thought to be due to gastric ulcer. For ten years he had cold feet and for four years cold, blue hands in winter. Examination showed no gross changes in the skull, but there was some bulging in the temporofrontal region. There were marked kyphosis and slight scoliosis, some thickening of the clavicles, thickening of the right humerus, slight outward bending of both forearms, a wide costal angle, a diamond-shaped abdomen, marked forward and outward bending of both femora, forward bending of the tibiae, gross thickening of the right tibia and genu extrorsum, the condyles being separated by 4 inches (10.2 cm.). Examination of the cardiovascular system showed gross thickening and tortuosity of the radial and brachial arteries, with visible pulsation; slight tortuosity of the temporal vessels; the apex beat in the fifth space ½ inch (1.27 cm.) from the midclavicular line; marked accentuation of the aortic second sound but no murmur; a blood pressure of 140 systolic and 90 diastolic by Pachon's method or by the mercury manometer. The blood pressure in the right ankle was 270 systolic and 150 diastolic; in the left, 220 systolic and 130 diastolic. Oscillometric oscillations indicated patency of the tibial arteries. There were medium moist sounds at the bases of both lungs. The central nervous system showed no abnormalities except loss of the sense of vibration in both lower limbs. Roentgenography showed marked changes characteristic of osteitis deformans in all the bones; the tibial vessels were visible in the roentgenogram. Examination of the blood showed a urea content of 0.04 per cent. A blood count showed 4,900,000 cells, with 60 per cent hemoglobin and a color index of 0.61 per cent. The leukocytes numbered 3,760, with 69.5 per cent neutrophils, 1 per cent eosinophils, 23 per cent small lymphocytes, 0.5 per cent large lymphocytes, 5.5 per cent large hyaline cells and 0.5 per cent granular basophilic cells.

CASE 29.—Y. V., a woman, aged 69, entered the hospital with a history of dyspesia of three years' duration simulating that of gastric ulcer. She had epigastric pain one and one-half hours after meals with periodicity. She had chronic bronchitis. Examination showed moderate enlargement of the skull, with bulging of the occipital and parietal regions, which was greater on the right than on the left; moderate kyphosis and genu varum, with outward bending of the femora and forward bending of the tibiae, which was greater on the left than on the right. Examination of the cardiovascular system showed: moderate thickening of all the arteries; tortuosity of the temporal vessels; a blood pressure of 140 systolic and 80 diastolic; the apex beat in the fifth space of the midclavicular line, and a sys-

tolic murmur at the apex of the heart. Scattered bronchi were audible throughout the lungs. Roentgenography showed typical changes in the femora, tibiae and skull. A blood count showed 4,900,000 erythrocytes, with 73 per cent hemoglobin and a color index of 0.74 per cent, and 4,880 leukocytes, with 42 per cent neutrophils, 1 per cent eosinophils, 43 per cent small lymphocytes, 6.5 per cent large lymphocytes, 6.5 per cent large hyaline cells and 1 per cent coarsely granular basophils.

CASE 30.—H. L., a man, aged 63, had aching in the right thigh for three years. For two years he had noticed outward bending of the left leg below the knee. A few months before examination he sustained a pathologic fracture of the left tibia while running. The skull was apparently normal on examination. There were outward and forward bending and gross thickening of the periosteum of the left tibia, and slight bending of the right tibia and of the right femur. No gross abnormalities were found on examination of the cardiovascular system. The blood pressure was 120 systolic and 80 diastolic. Roentgenograms of the tibia and femur showed osteitis deformans.

CASE 31.—D. R., a man, aged 72, was admitted to the hospital because of vesical calculus. Frequency of urination and dysuria had been present for several years. Roentgenography of the bladder incidentally revealed changes characteristic of osteitis deformans in the pelvic bones and lumbar segments of the spine. Subsequent questioning elicited a history of stabbing pains in the feet and legs, which ran parallel to the long axis of the limbs and had occurred over a period of thirty years. During the last few years the back had become bent. Periodic frontal headaches associated with vomiting and suggestive of migraine had occurred up to the age of 40. Twenty-five years before the patient was examined, fracture of the left clavicle had occurred. Examination revealed gross kyphosis and some scoliosis; there were no other obvious changes. Examination of the cardiovascular system showed thickening, tortuosity and visible pulsation of the radial and brachial arteries; indefinite capillary pulsation; the apex beat in the fifth space 1 inch (2.54 cm.) external to the midclavicular line; a diastolic murmur in the mitral area, and accentuation of the aortic second sound. The blood pressure was 140 systolic and 80 diastolic; below 80 the pulsations were heard down to 0, but with markedly diminished intensity. The temporal vessels were not tortuous. Examination of the central nervous system showed loss of the vibratory sense in the right leg and a fibrillary tremor in both calves. Both hands showed evidence of chronic arthritis.

CASE 32.—J. H., a man, aged 52, had osteitis deformans plus spastic paraplegia. Eighteen months before examination he had noticed occasional twitching of the lower limbs; this occurred about once a week and lasted for one second or longer. The twitching consisted of a short jerk of the whole limb. Nine months before examination he experienced a gnawing pain (likened to lumbago) at the lower part of the back. This pain continued constantly and was worse on bending. Five months before examination the patient awoke in the middle of the night with pins and needles sensations in the right calf, and at that time he observed weakness of the right leg. In the morning the left leg also became weak; on attempting to rise the patient found that he could walk only with difficulty, and he was forced to return to bed. Within three days complete paralysis of both lower limbs gradually developed. At this time retention of urine and complete constipation also occurred. Catheterization was necessary for three weeks, during which time the patient was "light-headed," had attacks of violence and was unable to recognize friends. Cystitis, bed sores and thrombosis of the left femoral vein were complications.

The medical adviser stated that at the onset the patient had had complete flaccid paralysis of both legs and anesthesia up to the costal margin. After a few weeks there had been gradual improvement; power and sensation had partially returned in the legs, with some simultaneous recovery of sphincter control. At that time a troublesome bronchitis had developed, and the patient suffered from "heart attacks," with a rapid, irregular pulse, which was controlled by digitalis. Since the acute attack the condition of the patient had gradually improved in all respects. He was, however, unable to walk, although the sphincter trouble had disappeared. A numb, dragging feeling in both legs had persisted. The backache had disappeared with the onset of paralysis. Examination showed a well developed, healthy looking man. There was no gross alteration of the skull, but the occipital and temporal regions showed a slight bulging. Decubitus valgus was present and was more marked on the right. There was some widening of the costal angle. There were also slight forward and outward bowing of both femora, particularly of the right, and moderate kyphosis, with rigidity of the lower thoracic and lumbar regions. On the whole, the changes in the skeletal system were not particularly marked on clinical examination. Examination of the central nervous system showed normal disks, pupils and cranial nerves. There was no abnormality of the upper limbs, the reflexes being present and equal. The abdominal reflexes were present and equal. The lower limbs showed marked spastic paraplegia in flexion; the knee and ankle jerks were grossly exaggerated; the Babinski reflex was obtained in both feet, and ankle clonus was present. Postural sensibility was absent, and the vibratory sense was greatly diminished in both legs. There was inability to appreciate cotton-wool, pinprick, heat and cold below the fourth lumbar vertebra, with relative impairment of sensation above this level. Sensation was found to approach normal gradually as examination ascended to the level of the tenth thoracic segment. Jerky involuntary movements of the lower limbs occurred at intervals of from one to three minutes. There was no marked wasting. While the patient was in the hospital the paraplegia became more severe, with the disappearance of reflexes. Incontinence of the urine and feces also developed. Permission to perform laminectomy was refused by the patient. Examination of the cardiovascular system showed that the arteries of the arm were moderately thickened; there was some tortuosity of the temporal vessels. The heart was normal. The blood pressure was 165 systolic and 100 diastolic. The Wasermann reaction was negative for the blood and the spinal fluid. The spinal fluid was clear, with no cobweb; it contained 1 white cell per cubic centimeter, but there was a marked excess of protein—0.3 per cent. Roentgenography showed definite and extensive thickening of the vertebrae, especially of the sacral and iliac bones; the changes were those of osteitis deformans. There was much lipping in the thoracic region. The appearance of the skull was only suspicious, there being a few areas of thickened patches in the vertex. The right femur showed thickening in the upper portion and a cotton-wool appearance in the middle portion, with suggestive changes in the lower third. The tibiae, radii and ulnae showed slight changes. The roentgenographic diagnosis was osteitis deformans.

Case 33.—F., a man, aged 60, gave a history of gradual enlargement of the skull, bowing of the legs and stooping, of many years duration. He had suffered from recurrent ascites for several years. Examination revealed gross enlargement of the skull, with bulging of the frontal and temporal regions; a wide costal angle; very gross outward and forward bending of both femora and both tibiae; genu extrorsum, and meningocele in the midfrontal region. Cardiovascular findings were: moderate thickening of the radial and brachial arteries, with

tortuosity of the temporal vessels; a blood pressure of 135 systolic and 80 diastolic; the apex beat in the fifth space, ½ inch (1.27 cm.) from the external midclavicular line, and a systolic murmur in the mitral area. There was bilateral deafness of the middle ear. Examination of the central nervous system showed lateral nystagmus in both directions. The cranial nerves otherwise were normal. The upper limbs were normal. The abdominal reflexes were present and equal; the knee jerks were present and equal; the right ankle jerk was not obtained, while the left ankle jerk was just present. The plantar reflexes were normal, and postural sensibility was normal. Examination of the abdomen showed an enlarged liver one handbreadth below the costal margin. Gross ascites was present. Roentgenography showed typical changes in all the bones. The Wassermann reaction was negative.

Case 34.—F. H., a man, aged 54, in 1921 noticed some stiffness of his knees, which impeded walking and necessitated stopping on the pavement. The pain disappeared when the patient sat or lay down and was attributed to rheumatism. This condition continued until three months before examination (April, 1927), when the stiffness increased over a period of a few days, after which there occurred a sudden and dramatic loss of the use of both legs when the patient was on the way home. He stated that he sank to the ground several yards from his house and literally crawled home. Since that time he would not trust himself to walk, as his knees might become stiff at any moment and he would collapse. He had been treated with hot air baths, massage and ultraviolet rays, without any obvious effect. His general appearance was that of a healthy man; the skull was enlarged, with well marked supra-orbital ridges. The patient wore a hat size 7⅛, whereas eighteen years before he had worn size 6¾. The circumference of the head at the time of examination was 22¾ inches (57.8 cm.). Both clavicles were enlarged, the right to a greater degree than the left. There were slight kyphosis, a wide subcostal angle, with splaying of the lower ribs, and a transverse indentation in the midthoracic region. The upper limbs were not obviously affected. The lower limbs showed genu extrorsum, with both patellae turned outward. Both femora rotated outward and showed an external and slightly forward convexity. The internal condyles were separated by 3 inches (7.6 cm.). There was some limitation of movement at both hip joints, especially on the left. The upper and lower ends of the tibiae appeared to be thickened; some crepitations were heard when the knee joint was moved. Examination of the central nervous system revealed that the left pupil was slightly larger than the right; the fundi and the cranial nerves were normal. The supinator, biceps and triceps jerks were produced and were equal. There was no dystonia, wasting, ataxia, loss of power, sensory loss or absence of postural sensibility in the upper limbs. The abdominal reflexes were not obtained. Spastic paresis of both lower limbs was found, which was greater on the right than on the left; the spasticity was especially marked in the adductor muscles. The knee jerks were slight and were greater on the right than on the left. The ankle jerks were not obtained. The Babinski plantar reflex was elicited on both sides. There were marked fibrillation and twitching of the quadriceps muscles and hamstring tendons, with generalized wasting. All the movements of the lower limbs were weak, especially those of the extensors of the knee joints, and dorsiflexion of the ankle was present. Relative analgesia and anesthesia to pinprick and cotton-wool respectively was present over the fourth and fifth lumbar segments, involving the sacral areas to a less extent and extending higher than the fifth lumbar segment, with a gradual decrease in severity up to the third thoracic segment. There was defective appreciation of heat and cold over approximately the same area; heat was not

felt at all as such, and in addition there was some confusion between hot and cold stimuli. Postural sensibility was absent on the right side and was impaired on the left. The vibratory sense was lost over the fourth and fifth lumbar segments. The patient was unable to stand with any stability and would fall if he attempted to walk; this instability was worse with the eyes closed. Examination of the cardiovascular system showed: moderate thickening of the arteries, with tortuosity of the temporal vessels; a blood pressure of 140 systolic and 70 diastolic; the apex beat in the fifth space of the midclavicular line; accentuation of the aortic second sound, and a systolic murmur at the base and apex of the heart. The lungs were normal. There was slight enlargement of the liver, and the prostate was moderately enlarged. A blood count showed: erythrocytes, 4,800,000, with 70 per cent hemoglobin and a color index of 0.72 per cent; leukocytes, 7,840, with 65.5 per cent neutrophils, 1 per cent eosinophils, 27 per cent small lymphocytes, 14.5 per cent large lymphocytes and 2 per cent large hyaline cells. Roentgenography showed typical changes of osteitis deformans in the spine, skull, femora, tibiae and clavicles; the radii and humeri were not affected.

AGE; SEX; FAMILIAL INCIDENCE

Age.—Osteitis deformans usually becomes manifest in middle life. It rarely occurs before the age of 30, but in one of Paget's [2] patients it began at the age of 28. Czerny's [1] patient was a man aged 22, and one of Stilling's [4] patients was first examined at 21 years of age. Roberts and Cohen [3] cited four supposed cases from the literature, in which the age of the patients was between 12 and 16, and they raised the pertinent question of mistaken diagnosis and of possible syphilis. Packard, Steele and Kirkbride [5] found the average age to be 61, the youngest patient they saw being 39 and the oldest, 82. Stilling recorded a case in a patient who was first seen at the age of 92.

In the series studied by us the average age of the patients when they were first examined was 55; the youngest was 39 and the oldest, 78. The average age of onset was 46; the youngest patient was 30 and the oldest, 60.

Sex.—Packard, Steele and Kirkbride found from a study of the literature that cases were reported in forty-one males and twenty-four females. In the series studied by Roberts and Cohen the incidence was about equal for both sexes. In our thirty-four cases there were eighteen females and sixteen males.

Familial Incidence.—Paget was unable to trace any inherited tendencies. Roberts and Cohen, however, cited thirteen cases of familial incidence from the literature, and two of their own patients were sisters. Apparently the condition has not been noted in more than two generations. The patients in cases 22 and 23 of our series were brother and

4. Stilling, H.: Virchows Arch. f. path. Anat. **119**:542, 1890.

5. Packard, F. A.; Steele, J. D., and Kirkbride, T. S.: Am. J. M. Sc. **122**: 552, 1901.

sister, and from their statements it is probable that their mother also suffered from osteitis deformans.

MODE OF ONSET

Osteitis deformans is usually insidious in its onset and may be present for many years without the patient being aware of anything unusual.

In ten patients of the present series the first symptom was pain in the lower limbs; in two, pain in the back, and in two, headache. Fracture of a bone was the first sign in four cases. In three patients bending of the lower limbs first attracted attention and in one, bending of the forearm. In two instances the patients were admitted to the hospital because of spastic paraplegia, and in six patients osteitis deformans was discovered only on roentgenographic examination for the following disorders: synovitis, prostatic disease, bronchitis, vesical calculus and appendicitis. It is therefore important to remember that patients with osteitis deformans do not necessarily show the classic picture of the disease, and, further, that gross changes of the skull may be lacking for many years. Roberts and Cohen were of the opinion that only half of their sixteen patients showed sufficient clinical evidence of Paget's disease before roentgenograms were taken.

PAIN IN OSTEITIS DEFORMANS

Paget stated that "in its earlier periods and sometimes through all its course the disease is attended with pains in the affected bones, pains widely various in severity, and variously described as rheumatic, gouty or neuralgic, not especially nocturnal or periodical."

Pain occurred in twenty-four of the thirty-four patients of our series. The pains were usually in the back and lower limbs, but eight patients complained of severe headache. The latter occurred in any part of the skull and was of variable character, for example, dull and shooting, nagging, throbbing or "maddening like a weight." Arteriosclerosis and hypertension ought to be considered as factors in the causation of headache in osteitis deformans, as they are frequently associated with it.

Pains in the lower limbs may be very severe. In some of our patients they were knifelike, shooting up and down the long axis of the limbs; they lasted only a few minutes but were followed by residual soreness of several hours' duration. The pains were sometimes sufficiently severe to cause the lower limbs suddenly to give way and the patient to fall. They might be worse on exertion or might awaken the patient at night. In some patients they were dull and aching.

Cramps in the calves sometimes occurred at night, or a sudden pain might compel the patient to stop walking, as in intermittent claudication. These pains were probably due to coincident arteriosclerosis in the peripheral arteries.

Other patients experienced pains in the joints, probably due to complicating arthritis.

Pain in the back may be very severe; it may be associated with a gradually increasing stooping posture and may be aggravated by the attempts of the patient to stand up straight.

Elting [6] suggested that pain in the long bones is due to distention of the periosteum. In some cases in this series pain was definitely associated with the changing shape of the bones and the development of new axes of strain and stress.

In several cases dried suprarenal extract in doses of 5 grains (0.32 Gm.) taken three times a day was very potent in relieving pain. Our attention was first drawn to this empirical therapy by Robert Milne. (Investigations of the effects of cortical extract parenterally administered are being carried out.)

SKELETAL CHANGES

There is little to add to the original description of Paget. The changes in the shape of the bones are dependent on softening and on the subsequent influence of gravity and muscular tension. The latter factor is well shown in patients 22 and 23 of the present series, a sister and brother. The brother was right-handed and had marked convex bending of the right radius. The sister was left-handed and had equally well marked bending of the left radius. The effect of gravity is shown by gradually increasing kyphosis, so that the face may habitually look toward the ground, and also by the bending of the femora and tibiae. The latter may be bent inward as well as forward so that they cross over one another, giving the appearance of scissor legs. This occurred in three of our patients (1, 9 and 10) and was so extreme in patient 10 that he had been unable to stand or walk for ten years. This is somewhat in excess of Paget's observations, as he wrote: "The limbs, however misshapen, remain strong and fit to support the trunk."

The wide pelvis has been frequently noted, but this is usually associated with a wide subcostal angle and splaying of the ribs. As the latter tend to approach the iliac crest, the bony boundary of the abdomen suggests the apposition of two faceted triangles—the diamond-shaped abdomen.

The classic picture of osteitis deformans, in which the patient resembles a simian-like ancestor, can hardly be mistaken. It is important

6. Elting, A. W.: Bull. Johns Hopkins Hosp. **12**:343, 1901.

to remember, however, that the skull may not be involved, at any rate, not for many years. Paget himself described such a case in a man, aged 51, in whom the disease began with changes in the tibia, but who showed no alteration in the skull ten years later. French [7] observed an almost identical case in a woman, aged 53. Packard, Steele and Kirkbride, from a review of the literature, found that of sixty-six patients, nine showed no enlargement of the head. Of our series of thirty-four patients, gross changes in the skull were absent in no less than eight. In one patient (5) the skull only was involved, but this was more obvious roentgenographically than clinically.

As regards the bone which is first affected, Locke [8] stated that this is "with few exceptions the tibia or the skull." Packard, Steele and Kirkbride found that in forty-nine cases (from the literature) the first bone involved was the skull in fourteen patients, one tibia in seventeen and both tibiae in thirteen. In the present series, apart from two cases in which the tibia showed changes five and seven years respectively before the other bones, evidence as to the sequence of skeletal changes was indefinite.

Fractures are not uncommon in osteitis deformans. They usually follow very slight traumas, but sometimes there is no obvious cause. Roberts and Cohen reported three fractures in sixteen cases. In a fourth patient roentgenography showed "no fewer than twenty incomplete fractures of the tibia on the convex anterior aspect." Fractures occurred in five patients in the present series; there was little or no preceding trauma in four patients. In three patients the femur was broken, and in two patients, the tibia. The ages of the patients at the time of fracture were 38, 44, 49, 54 and 63. In one patient (23) the neck of the femur was incompletely fractured, the injury resembling a green-stick fracture. The only complaint had been of aching of the thigh for one month, and neither the fracture nor osteitis deformans was suspected before roentgen examination. In one patient (2), a woman, aged 44, it was found necessary to plate the bone, as healing did not occur with external splinting. The fracture was in the middle third of the femur and had occurred while the patient was fastening her boot-lace. It is interesting to note that at operation the bone was found to be very soft. In another patient (4) the right femur was fractured six years after the left.

In regard to arthritis, Da Costa [9] stated that "the joints are scarcely ever involved in the disease." Roberts and Cohen, however, found

7. French, H.: Brit. M. J. **2**:1152, 1903.

8. Locke, E. A., in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1921, vol. 4, p. 408.

9. Da Costa, J. C.: S. Clin. North America **1**:47, 1921.

osteo-arthritis in seven of sixteen patients. Knaggs [10] discovered fairly frequent lipping of the vertebrae. Arthritis was present in at least three patients of the present series, but its presence is not regarded as of any significance, considering the age at which osteitis deformans commonly occurs.

Sarcoma developed in one patient (7) of the present series, the femur being the bone involved. Malignant changes were present in three of twelve of Paget's patients. Packard, Steele and Kirkbride, from a study of the literature, found sarcoma in five of sixty-seven patients, and Da Costa, from a similar study, noted sarcoma in fourteen of one hundred and fifty-eight patients.

LESIONS OF THE NERVOUS SYSTEM IN OSTEITIS DEFORMANS

Although the occurrence of nerve lesions in osteitis deformans has been noted by several authors, it is obvious from the diversity of the lesions that in the majority of cases they were merely coincidental: syringomyelia (Marie and Léri [11]), tabes (Chartier and Descomps [12]), bulbar palsy (Lunn [13]), Huntington's chorea (Mackey [14]), lesions of the basal tract and spinal cord (Madea and de Fano [15]), lesions of the medulla (Gilles de la Tourette and Marinesco [16]) and lesions of the medulla and peripheral nerves (Hudelo and Heitz [17]). In other cases one must consider the possibility of compression by bony deformity: degeneration of nerves entering the intervertebral foramina (Pitres and Vaillard [18]), lesions of the posterior and lateral columns (Levi [19]), chronic myelitis (von Recklinghausen [20]), increased reflexes and vesical disturbances (Pic [21]), spastic paraplegia (Azoulay, Lagrot and Ardin-Delteil,[22] and Wyllie [23]) and optic atrophy (Wyllie).

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10. Knaggs, R. L.: Inflammatory and Toxic Diseases of Bone, New York, William Wood & Company, 1926.
11. Marie, P., and Léri, P.: Bull. et mém. Soc. méd. d. hôp. de Paris **43**:904, 1919.
12. Chartier, M., and Descomps, P.: Nouv. iconog. de la Salpêtrière **20**:84, 1907.
13. Lunn, J. R.: Tr. Clin. Soc. London **18**:272, 1885.
14. Mackey, C.: Lancet **2**:787, 1906.
15. Madea, E., and de Fano, C.: Morgagni **47**:337, 1906.
16. Gilles de la Tourette, G., and Marinesco, G.: Bull. et mém. soc. méd. d. hôp. de Paris **2**:422, 1894.
17. Hudelo, and Heitz, J.: Nouv. iconog. de la Salpêtrière **14**:415, 1901.
18. Pitres, J. A., and Vaillard: Arch. d. physiol. norm. et path. **5**:106, 1885.
19. Levi, L.: Nouv. iconog. de la Salpêtrière **10**:117, 1897.
20. von Recklinghausen, F. D.: Untersuchungen über Rachitis und Osteomalacie, Jena, Gustav Fischer, 1910.
21. Pic: Gaz. d. hôp. de Toulouse, October, 1886.
22. Azoulay; Lagrot, and Ardin-Delteil: Bull. et mém. Soc. méd. d. hôp. de Paris **47**:920, 1923.
23. Wyllie, J. H.: Brain **46**:336, 1923.

Wyllie described two cases of paraplegia caused by compression, in which laminectomy was performed by Sir Percy Sargent. At operation "the bone was much thickened and softened. The perithecal space was absent, and the inner surface of the laminae lay in close apposition to the dura mater. Pulsation of the dura was at first very feeble but improved as the decompression was effected. In the patient who recovered from the operation, the paraplegic condition was greatly improved."

In two cases (32 and 34) of our series spastic paraplegia caused by spinal compression due to vertebral deformity was present. Both patients were admitted to the hospital because of possible spinal neoplasm. In patient 32 the first sign consisted of involuntary twitchings of the lower limbs. Subsequently pain occurred in the back and paresthesias of the lower limbs. Weakness began in the night, and within three days complete flaccid paralysis of the lower limbs, with retention of urine, had developed. Finally incontinence of urine, with spastic paraplegia, occurred. The sensory changes consisted of a gradually increasing impairment of sensation, descending from the level of the tenth dorsal vertebra, from partial loss to complete loss of sensation in the legs and feet. The cerebrospinal fluid was clear, showed no cobweb and contained 1 white cell per cubic centimeter and a marked excess of protein, 0.3 per cent.

In patient 34, apart from some preliminary stiffness of one knee, the onset was sudden weakness of the lower limbs. While he was walking home his legs gave way under him some yards from his house, and he was obliged to crawl home on all fours. Attempts at lumbar puncture were unsuccessful (as in one of Wyllie's cases), and this drew attention to bony changes in the spinal column and in other bones. The signs were those of spastic paraplegia, with sensory changes similar to those in patient 32. Permission for an operation was refused in both cases.

Seven other patients had evidence of nerve lesions, which were attributable to spinal compression or to vascular changes. Patient 5 had transitory paresis of both lower limbs, with relative analgesia. Patient 8 had involuntary twitching of the right foot; the reflexes in the lower limbs were increased but were equal on the two sides, and the plantar responses were equivocal. Patients 18, 20 and 25 had relative anesthesia and analgesia of the lower limbs, which gradually approached normal toward the trunk. Patients 28 and 31 had loss of vibratory sense in the lower limbs.

One patient (12) suffered from senile epilepsy. During the six months previous to examination he had three attacks of convulsions, with loss of consciousness. Generalized twitching occurred during the attack, without evidence of focal spread. The last attack resembled status epilepticus; there were repeated convulsions for four hours and a coma-

tose state persisting for two days. Examination revealed left hemiplegia, the upper limb being very much more involved than the lower. The blood pressure was not raised, but there were marked arteriosclerosis and hemorrhages in the fundi.

Two patients (2 and 20) had lateral nystagmus with diplopia. Three patients (21, 24 and 25) suffered from frequency of micturition.

Apart from mere coincidence, neurologic disorders in osteitis deformans are attributable either to compression caused by bony overgrowth or deformity or to arteriosclerosis.

PSYCHOSES IN OSTEITIS DEFORMANS

Paget,[2] in his original description, emphasized the absence of mental changes in osteitis deformans. "Even when the skull is highly thickened and all its bones exceedingly altered in structure the mind remains unaffected."

Since then, however, several instances of psychosis have been reported. The earliest was that of Lunn's [18] patient, a man, aged 75, who was in an institution for four years, the exact nature of the psychosis not being stated. Prince [24] described a case of delusional insanity in a woman, aged 44. Fussell [25] reported senile dementia in a man, aged 78. Mackey [14] described a case of Huntington's chorea in a man, aged 57, with mental deterioration, excessive emotionalism and impaired memory. Hann [26] had as a patient a woman, aged 60, with mental deterioration and attacks of unconsciousness. Paine [27] described a case in a man, aged 75, with hallucinations, delusions and dementia. Smith [28] described delusional insanity in a woman, aged 60, and the development of osteitis deformans in a woman, aged 80, who had been in an institution because of a psychosis since the age of 31.

Kaufman [29] cited three cases from the literature in which occurred: melancholia (Fitz [30]), psychosis and mental deterioration (Moynan [31]) and maniacal delirium with epilepsy (Marie [32]). He described four additional cases: delusions and hallucinations in a woman, aged 65, impaired memory and intellect and confusion in a man, aged 52, paranoia in a woman, aged 53, and an indefinite psychosis and suspected intracranial tumor in a woman, aged 46.

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24. Prince, M.: Tr. A. Am. Physicians **17**:392, 1902.
25. Fussell, M. H.: Tr. A. Am. Physicians **17**:406, 1902.
26. Hann, G. R.: Brit. M. J. **1**:135, 1910.
27. Paine, F.: Proc. Roy. Soc. Med. **6**:72, 1912-1913.
28. Smith, L. H.: J. Nerv. & Ment. Dis. **68**:578, 1928.
29. Kaufman, M. R.: Psychosis in Paget's Disease (Osteitis Deformans), Arch. Neurol. & Psychiat. **21**:828 (April) 1929.
30. Fitz, R. H.: Tr. A. Am. Physicians **17**:398, 1902.
31. Moynan, R. S.: Ohio State M. J. **24**:206, 1928.
32. Marie, A.: Encéphale **22**:475, 1927.

Hartfall [33] described delusional insanity in a man, aged 63. In eighteen other patients with osteitis deformans he found no evidence of mental change. Rutherford [34] reported delusional insanity in a man, aged 62.

In our series of thirty-four cases there were two instances (5 and 11) of mental abnormality: homicidal tendencies and periodic loss of memory in a man, aged 50, and delusional insanity and impaired intelligence in a woman, aged 70. Minor mental deterioration—for example, defective memory for recent events—is more common.

Psychologic alterations of this kind are probably no more common than in patients of middle age who have arteriosclerosis but who are unafflicted with Paget's disease.

CARDIOVASCULAR SYMPTOMS

Arterial degeneration is common in patients with osteitis deformans. Thus Knaggs [10] stated: "Atheromatous arteries are almost a constant feature in these cases, and are seen even when the disease occurs in middle age." Locke [8] was of the same opinion: "More or less generalised arterio-sclerosis may be regarded as an almost universal manifestation of the disease." Roberts and Cohen [3] observed that "one is impressed by the frequency of calcification of the arteries shown by x-ray."

Of the present series of thirty-four patients, nineteen showed severe arteriosclerosis; six, moderate, and four, slight; in four patients, however, there was no clinical evidence of arterial degeneration. The patients with severe arteriosclerosis were nearly all over 50 years of age.

It is possible that arteriosclerosis occurs more frequently in osteitis deformans than in a control group of patients of similar age, but there is not sufficient evidence to warrant the theory that toxins or abnormal calcium metabolism is the direct cause of the arterial degeneration.

Hypertension was present in thirteen patients, the systolic pressure being 180 or more in seven, and between 160 and 180 in six. Eighteen patients had a systolic pressure of 140 or less. Arteriosclerosis and hypertension were not infrequently dissociated, the former occurring without the latter and vice versa. This is in keeping with the findings in any group of patients.

Aortic incompetence was present in three patients, one of whom was suffering from syphilis.

In five patients with arteriosclerosis the diastolic pressure was indeterminate, pulsations being heard down to 0; a systolic murmur was

33. Hartfall, S. J.: Lancet **2**:68 (July 11) 1931.
34. Rutherford, W. J.: Lancet **2**:350 (Aug. 15) 1931.

present in the aortic area, and pulsation of the peripheral arteries was easily visible. On repeated examination, however, no aortic diastolic murmur could be detected. In only one of the five was hypertension present.

Bradycardia was present in one patient and auricular fibrillation in another.

In one woman, aged 68, who had arteriosclerosis, senile gangrene of the toes developed, and pulsation was absent in the posterior tibial and dorsalis pedis arteries. A periarterial sympathectomy by W. S. Perrin resulted in limitation of the gangrene and permitted a subsequent local amputation.

OPHTHALMIC AND AURAL SYMPTOMS

Ophthalmic Changes.—Paget [2] described the occurrence of retinal hemorrhages in osteitis deformans, and Watson [35] noted extensive choroidal changes. In three of Vergne's [36] patients there was well marked choroidoretinitis. Coppez [37] found degeneration of the retina in four patients, with the occurrence of diplopia in one. Roberts and Cohen [8] described choroiditis and retinal hemorrhage in one patient. Crystalline opacities were noted by Hurwitz,[38] Vergne and Coppez. Wyllie [23] recorded two cases with both optic atrophy and diplopia. He attributed the optic atrophy to compression of the optic nerve by bony overgrowth and the diplopia to injury of one or more of the ocular motor nerves by similar bony changes. Ormard [39] described choroiditis and hemorrhages in one patient, and Batten [40] stated that angioid streaks associated with choroidal disease had been noticed in Paget's disease by Juler and by Verhoeff.

In our series there were two patients with optic atrophy (5 and 10); in the former the atrophy was associated with diplopia; in the latter, with choroiditis. Diplopia also occurred in patients 2 and 20, together with nystagmus. Hemorrhages of the fundus were present in patient 12, and keratitis with corneal opacities in patient 11. Patient 1, who was shown before the meeting of the Association of Physicians, in 1930 by Dr. Evan Bedford, had subretinal hemorrhages. Mr. T. C. Summers reported that "surrounding the macula in a horseshoe-shaped manner, deep to the retina, is a large plum-shaped hemorrhage, seen in each eye, and probably situated in the choroid. At the macula were numerous folds with a few streak hemorrhages which, from their color, appeared to be

35. Watson, W. T.: Bull. Johns Hopkins Hosp. **9**:133, 1898.
36. Vergne, J.: Ann. d'ocul. **140**:321, 1908.
37. Coppez, I.: Arch. d'opht. **32**:529, 1912.
38. Hurwitz, S. H.: Bull. Johns Hopkins Hosp. **24**:263, 1913.
39. Ormard, A. W.: Lancet **1**:973, 1931.
40. Batten, R. D.: Brit. J. Ophth. **15**:279, 1931.

in the deeper layers of the retina. One surprising feature was that the retinal vessels appeared quite normal."

The ophthalmic changes in osteitis deformans are probably caused by (1) bony compression of the optic or the oculomotor nerves or (2) retinal arteriosclerosis. There is not sufficient evidence at present in favor of a hypothetic toxin.

Impairment of Hearing.—Locke [8] stated that "a gradual impairment of hearing in osteitis deformans is the rule." He considered that bony compression of the labyrinth is an important factor. Gregg [41] pointed out the possibility of pressure by bony overgrowth on any of the cranial nerves, including the auditory.

In our series ten patients had grossly impaired hearing, but in nine this was due to chronic disease of the middle ear. The remaining patient had bilateral otosclerosis.

BIOCHEMICAL OBSERVATIONS

According to Locke, if syphilitic lesions of the bones are excluded, osteitis deformans is the most common of the chronic diseases of bone. A similar statement was made by Da Costa.[9] Yet there are on record very few investigations of a biochemical nature dealing with this disease. We include under the term "biochemical investigations" the study of such questions as the balance between the intake and output of dietary constituents, whether dietary deficiencies (or excesses) play a part in the onset of the disease, whether any abnormal changes occur in the nature and amount of the various chemical constituents of the tissues, particularly of the bones and of the blood, and to what extent such changes are specific for the disease. A brief account of what has already been done in the biochemical field will be given in the following paragraphs.

Changes in Chemical Composition of the Tissues.—(a) Bones: The most obvious pathologic changes in osteitis deformans are those in the bones, and a few chemical observations have been made by various investigators on specimens of bones obtained post mortem from patients with this disease. One of the almost invariable general observations is an increase in the percentage of organic matter and a diminution in the percentage of mineral matter (ash) in the bones. The fat content is usually increased. Whereas normal bone was found by Locke to have 37.8 per cent of organic matter, every bone in the patients with osteitis deformans which he studied showed organic matter varying between 42.6 and 48.5 per cent. The percentage of calcium content of the bone was invariably below normal, as was the magnesium content. The

41. Gregg, D.: Neurologic Symptoms in Osteitis Deformans (Paget's Disease), Arch. Neurol. & Psychiat. **15**:613 (May) 1926.

diminution in the latter was striking; while the normal value is in the region of 0.8 per cent, the values found for magnesium oxide in the bones of persons with osteitis deformans varied between 0.14 and 0.68 per cent.

Hunter [42] quoted Turnbull as stating that there is only one definite histologic difference between osteitis deformans (Paget) and generalized osteitis fibrosa (von Recklinghausen). In the former disease there is tremendous resorption of bone associated with great apposition, the apposition preponderating, while in the latter disease the essential change is widespread resorption of bone, apposition being focal and relatively insignificant. From the figures already quoted it appears that the bone laid down in osteitis deformans is abnormal not only in architecture but also in chemical composition.

(*b*) Blood: Hunter [42] stated that in Paget's disease the serum calcium and the plasma phosphorus are approximately normal. This differentiates the disease from generalized osteitis fibrosa, in which the serum calcium is almost invariably above and the plasma phosphorus below normal. However, although there are, unfortunately, few records of these determinations in true Paget's disease, the tendency is for the calcium to be a little below and the phosporus a little above normal. In a group of twelve patients with osteitis deformans the serum calcium varied between 8.2 and 9.8 mg. per hundred cubic centimeters, with an average of 9.1 mg., while the plasma phosphorus varied between 2.7 and 5.3 mg., with an average of 3.7 mg. Normal figures for serum calcium by the method used (Clark-Collip) are usually between 9 and 11 mg., with an average of about 10 mg. For plasma phosphorus, the average is about 3.3 mg. If there is any real variation from the normal in either serum calcium or plasma phosphorus in Paget's disease it must be small.

From the content of calcium and phosphorus in the blood there is no definite evidence of any parathyroid disturbance, and most pathologists are agreed that it is unusual to find signs of increased parathyroid activity post mortem.

The most striking biochemical difference that has been found (Kay [43]) between the blood of patients with osteitis deformans and that of normal persons is the greatly increased phosphatase activity in the plasma in the former. It has already been reported by Kay [43a, b] that this enzyme is present in relatively large amounts (twice the normal or more) in generalized diseases of the bone other than osteitis deformans, namely, in generalized osteitis fibrosa (two cases), in osteomalacia (two

42. Hunter, D.: Quart. J. Med. **24**:433, 1931.

43. Kay, H. D.: (*a*) Brit. J. Exper. Path. **10**:253, 1929; (*b*) J. Biol. Chem. **89**:249, 1930; (*c*) ibid., p. 235; (*d*) Physiol. Rev. **12**:384, 1932.

cases), in renal rickets (two cases), in adolescent rickets (one case) and in infantile rickets (in at least eight of ten cases). In almost all types of disease which did not involve the bone or in which the lesions of the bones were purely local, the phosphatase was either normal or slightly increased. The large rise in the phosphatase content of the plasma was thus almost specific for generalized disease of the bones.

*Plasma Phosphatase in Osteitis Deformans**

Case	Age, Years	Sex	Diagnosis	Duration, Years	Plasma Phosphatase Value†
1	57	F	Osteitis deformans, extensive changes	17	At least 3.00
2	44	F	Osteitis deformans, moderately extensive changes	6	At least 1.00
3	40	M	Osteitis deformans and meningovascular syphilis	2	At least 1.30
4	62	M	Osteitis deformans, moderately extensive	5	1.50
5	50	M	Osteitis deformans, unsuual type, skull only; changes in skull only seen on roentgen examination; no other skeletal changes	?	0.40
6	49	F	Osteitis deformans, moderate changes only	5	1.30
8	49	F	Osteitis deformans, almost entirely in skull, marked	10	At least 1.30
9	54	F	Osteitis deformans, marked in all bones	11	At least 3.00
10	60	M	Osteitis deformans, extensive	30	At least 2.50
13	39	F	Osteitis deformans, skull, clavicles, spine	2	At least 2.50
14	41	M	Osteitis deformans, extensive changes in all bones	6	At least 1.40
15	60	M	Osteitis deformans, all bones involved	8	At least 2.80
19	52	M	Osteitis deformans, many bones affected	Several	At least 1.40
20	71	M	Osteitis deformans, general	6	At least 0.80
21	55	F	Osteitis deformans, many bones affected	5	At least 1.20
23	49	M	Osteitis deformans, familial	10	0.66
25	50	M	Osteitis deformans, many bones and skull slightly affected	5	1.13
L. 1	65	M	Clinically, carcinomatosis; roentgenologically, doubtful Paget's disease	2	0.43
26	54	F	Osteitis deformans, many bones affected but not skull	Several	1.20
28	69	M	Osteitis deformans, extensive changes	Several	At least 0.70
29	69	F	Osteitis deformans, extensive changes	3 (?)	1.90
30	63	M	Osteitis deformans, limited to bones of leg	3	1.30
L. 2	49	M	Osteitis deformans, slight changes only	3	At least 0.65
T. 1	64	F	Osteitis deformans, extensive changes	Several	1.70
T. 2	35	M	Osteitis deformans, marked changes, limited to bones of leg	?	At least 2.25

* The peak of the distribution curve for normal persons is 0.14; for persons with diabetes, from 0.17 to 0.21; for persons with renal disease, from 0.18 to 0.21; for persons with arthritis, 0.13; for persons with a neoplasm (excluding a renal neoplasm), 0.21; for persons with hyperthyroidism, 0.41, and for those with osteomyelitis, 0.27.

† Milligrams of phosphorus liberated from sodium glycerophosphate under standard conditions by 1 cc. of plasma.

The rise in the phosphatase of the blood in osteitis deformans was corroborated by Roberts,[44] who used whole blood for his determinations.

In all the thirty patients with Paget's disease in whom we determined the phosphatase content the value for plasma phosphatase was much above the normal, and in the majority of cases it was more than ten times the normal. It is worthy of note that in one of the two cases in which the plasma value was below 0.6 unit the diagnosis of Paget's disease was doubtful.

44. Roberts, W. M.: Brit. J. Exper. Path. **11**:90, 1930.

The method of determination of phosphatase used by us is that described by Kay.[43c] The possible significance of the dramatic increase in plasma phosphatase in generalized disease of the bones and the connection of this agent with the similar enzyme which is known to occur in relatively large amounts in normal bone have recently been discussed by one of us (Kay [43b, d]), and there is at present little to add, except to mention that the rise is capable of reversal after suitable treatment in certain cases of osteomalacia and generalized osteitis fibrosa. But so far we have not observed any definite diminution in plasma phosphatase in Paget's disease, either with or without treatment. Roberts [44] stated that he was unable to diminish the high phosphatase content of whole blood in osteitis deformans by any method of therapy which he employed.

Although the phosphatase content is definitely high in every patient with osteitis deformans examined, even when the history is short and the disease is in the early stages, yet there is a rough correlation between the amount of the enzyme per unit volume of plasma and the severity of the disease, in that the cases which, clinically speaking, are milder usually show lower values than the more severe or extensive cases, the latter invariably giving high values. The phosphatase content remains high for the duration of the disease; for example, in one case of eight years' standing, in another of seventeen years' and in another of thirty years' standing, the level of phosphatase was about the same as in a severe case of only two years' duration.

Of the twenty-five cases enumerated in the table, twelve have already been reported briefly as having shown a high content of plasma phosphatase (Kay [43b]). These cases are included in this table as they have since been studied more thoroughly from a clinical point of view and in several instances the plasma phosphatase has been redetermined. The remainder are cases which were not previously studied for the determination of this enzyme. In spite of the high phosphatase content of the plasma, the urinary excretion of the enzyme, which has been determined in a few instances, remains low. The fecal excretion of the enzyme has not been followed.

The phosphorus partition in the blood was determined in one case only (13) by the method described by Kay and Byrom.[45] The figures were as follows: total acid-soluble phosphorus, *27.2* mg. per hundred cubic centimeters of blood; organic acid-soluble phosphorus, 23.9 mg. The hematocrit reading was 38.5 per cent corpuscles; the phosphorus index was 62, or slightly above normal. In three cases the phosphoric ester content of the plasma was determined and was found to be normal.

45. Kay, H. D., and Byrom, F. B.: Brit. J. Exper. Path. **8**:240, 1927.

The method of phosphatase determination just described was recently applied by Race,[46] who found that in a fairly large group of patients in whom disease of the bone was suspected, the method was of value as an aid in diagnosis in the early stages before the clinical symptoms were sufficiently advanced to permit a positive statement. O'Reilly and Race,[46a] in an interesting recent article described findings obtained for serum calcium, phosphorus and phosphatase in twenty-one cases of osteitis deformans. They found that, whereas the serum calcium and phosphorus are usually within normal limits, the phosphatase is always increased. The suspension stability of the blood is normal.

Changes in Mineral Metabolism.—With such obvious disturbance in skeletal structure it is only to be expected that the mineral metabolism will be severely disturbed during the course of this disease. We ourselves have not conducted any experiments on metabolism, but take this opportunity of bringing together a short summary of the results obtained in the few cases of Paget's disease in which experiments of this nature have been made.

In 1904, McCrudden, Goldthwait, Painter and Osgood[47] (quoted by Da Costa, Funk, Bergeim and Hawk[48]) found a retention of 6 per cent of calcium during a seven day period in a patient with osteitis deformans. Gruner, Scrimger and Foster,[49] while studying a patient suffering from osteitis deformans, found a loss of nitrogen, phosphorus, calcium and magnesium. Complete analyses of the feces were not made. However, sarcomas were developing at the same time, and the patient died in a very emaciated condition a few months later. It is doubtful whether the results of this investigation have much bearing on metabolism in an uncomplicated case of Paget's disease.

Da Costa and his associates[48] made a thorough metabolic study in two cases of osteitis deformans, one advanced, the other in the early stages. In both cases there was pronounced retention of calcium; in one case 50 per cent of the daily ingestion of 1.6 Gm. (reckoned as calcium oxide) was retained; in the other, 18 per cent of the daily ingestion of 2.6 Gm. was retained. This is the opposite of the findings in osteitis fibrosa. In both cases the amount of calcium excreted in the urine was much lower than normal. In normal persons about 10 per

46. Race, J.: Arch. M. Hydrol. **10**:6, 1932.

46a. O'Reilly, T. J., and Race, J.: Quart. J. Med. **1**:471, 1932.

47. McCrudden, F. H.; Goldthwait, J. E.; Painter, C. F., and Osgood, K. B.: Am. Med. **7**:547, 1904.

48. Da Costa, J. C.; Funk, E. H.; Bergeim, O., and Hawk, P. B.: Pubs. Jefferson M. Coll. & Hosp. **6**:1,1915.

49. Gruner, O. C.; Scrimger, F. A. C., and Foster, L. S.: A Clinical and Histologic Study of a Case of Paget's Disease of the Bones with Multiple Sarcoma Formation, Arch. Int. Med. **9**:641 (June) 1912.

cent of the excreted calcium is found in the urine, but in one of these patients only 4.6 per cent, and in the other, only 1 per cent, of the total amount of calcium excreted was found in the urine. This, again, is the opposite of what occurs in generalized osteitis fibrosa. White also reported a case in which the amount of calcium excreted in the urine was markedly subnormal.

Phosphorus was also retained in both patients of Da Costa and his associates. The first patient retained 33 per cent of a daily intake of 4 Gm. (reckoned as phosphorus pentoxide), the second, 29 per cent of a daily intake of 4.3 Gm. The same was true of magnesium; 59 per cent of a daily ingestion of 0.4 Gm. was retained in the one case, and 35 per cent of a daily intake of 0.6 Gm. was retained in the second. Sulphur and nitrogen, on the other hand, were lost in the first (severe) case to the extent of 44 per cent of the intake of 0.6 Gm. of sulphur and 1 per cent of the intake of 9 Gm. of nitrogen, but the second patient retained a little sulphur and nitrogen.

Locke stated that in two of his patients on whom metabolic studies were carried out retention of calcium (19.4 per cent and 11.5 per cent) and of magnesium (19.9 per cent and 10.9 per cent) were observed. He did not find, however, that the amount of calcium excreted in the urine was abnormal.

Another careful study, this time of a single typical case of osteitis deformans, was made by Cuthbertson.[50] His results confirm those of Da Costa and his associates. There was a retention of 15 per cent of the intake of calcium, of 7 per cent of the intake of phosphorus and of 10 per cent of the intake of magnesium. As in the severe case studied by Da Costa and his associates, there was a distinct loss of sulphur, to the extent of 17 per cent of the ingested sulphur.

Both Da Costa and his associates and Cuthbertson arrived at the conclusion that new tissue was being laid down in osteitis deformans which was relatively richer than normal bone in calcium and magnesium and poorer in phosphorus. A portion of this retention might be concerned with the calcification of the arteries which was proceeding, and Da Costa and his associates quote Selig's[51] statement that there is relatively much more magnesium in calcified arteries than in bone.

In summing up the situation with regard to mineral metabolism, Da Costa and his collaborators suggested that in advanced osteitis deformans the first step in the new formation of bone or osseous tissue is the production of a highly sulphurized organic matrix, which is transformed gradually by a process of calcification accompanied by the deposition of calcium, magnesium and phosphorus. During this deposition the sulphur

50. Cuthbertson, D. P.: Glasgow M. J. **108**:218, 1927.
51. Selig, A.: Verhandl. d. Cong. f. inn. Med. **25**:333, 1908.

of the matrix is replaced to a lesser or greater extent by the other elements mentioned, producing the results found experimentally, namely, retention of calcium, magnesium and phosphorus and loss of sulphur. These investigators suggested that a chronically somewhat decreased activity of the thyro-parathyroid mechanism may be concerned in the etiology of osteitis deformans. They pointed out that the metabolic picture of osteitis deformans is to a certain degree the reverse of that seen in parathyroid hyperplasia. If this theory is strong enough to bear additional speculation, it may be remarked that it has been shown that the amount of functional parathyroid tissue appears to vary greatly in apparently normal animals of the same species (Taylor, Weld, Branion and Kay [52]). This may be true for man and may be the congenital factor which is concerned in the not infrequently familial character of Paget's disease. Nevertheless, so far as we are aware, no cases of Paget's disease have been recorded following partial thyroidectomy with its usual accompanying loss of parathyroid tissue.

We may summarize our biochemical information with regard to osteitis deformans as follows:

1. There is a diminished percentage of ash in the bone, which contains a much smaller percentage of calcium and magnesium than normal (Locke), though, owing to the immense size of the bone, the total calcium and magnesium content may be greater than normal.

2. The serum calcium is not increased above normal but may, on the contrary, be slightly below normal. The plasma phosphorus is possibly slightly above normal. The plasma phosphatase is almost without exception definitely increased.

3. In two advanced cases (that of Da Costa and his associates and that of Cuthbertson) there was pronounced retention of calcium, magnesium and phosphorus in the body, with loss of sulphur. In one milder case there was a less marked retention of calcium, magnesium and phosphorus with no loss of sulphur.

ETIOLOGY

Paget [2] believed osteitis deformans to be a chronic inflammation, as the term indicates. Knaggs [10] thought that a toxin is responsible. Jefferson [53] suggested "an upset of internal secretion, thyro-parathyroid." Roberts and Cohen [8] noted that in a few cases changes had been observed in the parathyroid gland at autopsy, but they quoted Erdheim's [54] view that the changes are secondary to increased calcium

52. Taylor, N. B.; Weld, C. B.; Branion, H. D., and Kay, H. D.: Canad. M. A. J. **25**:28, 1931.

53. Jefferson, G.: Brit. J. Surg. **3**:219, 1915-1916.

54. Erdheim, J.: Frankfurt. Ztschr. f. Path. **7**:175, 1911.

metabolism and are not etiologically connected with Paget's disease. The estimations of calcium in our series do not give any definite indication of constant hyperactivity or hypo-activity of the parathyroid glands. There is, perhaps, some suggestion of varying activity of these glands in different phases of the disease, although adequate biochemical examination of the calcium balance over long periods is the only method of determining this with certainty. Clinical and pathologic evidence indicates phases of softening and hardening of the bones, rarefaction and excessive calcification. Further, the same bone or different bones may show evidence of different phases of the pathologic processes. If the parathyroids or other ductless glands are primarily at fault, it would be difficult to explain cases in which only one bone was involved for as long as ten years. One would expect a constant generalized involvement, such as occurs in osteitis fibrosa associated with hyperparathyroidism. In the latter condition the content of blood calcium is almost invariably above normal and the content of blood phosphorus is low (Hunter [42]). This is not so in osteitis deformans. Erdheim suggested that any changes in the activity of the parathyroids that can be demonstrated are probably secondary to the gross bony changes that are occurring. Certainly there is insufficient evidence at present to support the hypothesis that parathyroid dyscrasia is the sole factor in the production of osteitis deformans. The hypothesis of a low grade chronic inflammation, although acceptable from some points of view, is not susceptible of easy proof.

A syphilitic origin of osteitis deformans has been urged by Lannelongue,[55] Fournier [56] and many other French investigators. Da Costa and his associates, from a study of the literature, found that a positive Wassermann reaction was obtained in seven cases and a negative reaction in twenty-seven cases. Roberts and Cohen found that only two of their seventeen patients gave a positive Wassermann reaction. Elsner [57] stated that no patient with an uncomplicated case of Paget's disease has given a positive Wassermann reaction. In our series of thirty-four patients, positive Wassermann reactions were obtained in three. We believe, therefore, that the evidence is definitely against the suggestion of a syphilitic origin of osteitis deformans.

A neurotrophic origin of osteitis deformans has also been advanced. Thus, in 1883, Lancereaux [58] suggested that the nervous system plays an important rôle in the production of osteitis deformans. In 1894, Gilles de la Tourette and Marinesco,[16] and, in 1902, Prince,[24] urged the

55. Lannelongue, M.: Bull. Acad. de méd., Paris **49**:299, 1903.

56. Fournier, M.: Bull. Acad. de méd., Paris **49**:532, 1903.

57. Elsner: New York State J. Med. **10**:287, 1910.

58. Lancereaux, E.: Traité d'anatomie pathologique, Paris, A. Delahage & E. Lecrosnier, 1885, vol. 3.

etiologic significance of the changes in the central nervous system. It is true that the neurotrophic origin of bony changes is accepted in tabes and syringomyelia and that lesions of the central nervous system have been described in osteitis deformans. The latter, however, are so diverse in their character and distribution as to render their etiologic significance doubtful. It is much more reasonable to regard them either as the result of compression or of arteriosclerosis or as merely coincidental.

ROENTGENOLOGIC SECTION

BY G. E. VILVANDRÉ

The roentgen changes in typical Paget's disease are characteristic and are easily recognized. The roentgenologic detection of cases unsuspected clinically and the more difficult differential diagnosis deserve discussion.

On several occasions patients who were referred to the x-ray department of the London Hospital for renal or urinary calculi were found to exhibit bony changes in the pelvis characteristic of osteitis deformans. The "cotton-wool" changes immediately attract attention. There may be enlargement of the whole pelvis, with encroachment on its cavity, and flattening may be present. Rarefaction is seen side by side with increased density in the iliac bones—a combination of osteoporosis and hyperostosis, destructive osteitis and productive osteitis. The neck of the femur may also be increased in width and density and may lose its sharpness of outline.

The lumbar part of the spine shows thickening, increased density and loss of sharpness, but the contrast of the areas of rarefaction and sclerosis is nothing like that in the pelvis, where the ischiopubic rami may show a marked increase in width and alteration in bony texture. At first sight the lower portion of the pelvic girdle may suggest carcinomatosis, but the increase in width and the patchy sclerosis are opposed to such a diagnosis. In Paget's disease both the medullary and the cortical portion may become involved. The new bone is at first osteoid, but it may become calcified, and softening may be followed by regained rigidity. Owing to the formation of new bone in osteitis deformans the skeleton increases in width, a change not present in secondary carcinomatosis, and a distinguishing feature.

The earliest evidences of metastatic carcinoma from the prostate are noted in the ilium along the margins of the sacro-iliac synchondrosis and give rise to an increased density of the bone. Such a condition must be differentiated from Paget's disease. Confusion of these conditions has not been an uncommon mistake. The more commonly affected bones are the pelvis, tibia and cranium. In the cases which came under observation because of the possible presence of calculus the clinical appearance of osteitis deformans was absent or slight. Occasionally,

Fig. 1.—Roentgenogram of the pelvic bones of a patient with osteitis deformans, showing increase in density, striations and cotton-wool appearance. The ilium and femur on the right side show osteoclastic changes, and fracture has taken place through the neck of the right femur.

Fig. 2.—Roentgenogram showing the osteoclastic condition of the right femur and changes in the upper part of the tibia in the same patient as in figure 1.

patients with indefinite rheumatic pains have shown roentgenographic evidence of osteitis deformans, although clinically there was little to support the diagnosis. In some cases there has been no obvious enlargement of the skull; yet roentgenographic examination has revealed changes characteristic of osteitis deformans. The complication of the formation of sarcomatous tumors has been rare. In one case tumors of this kind occurred in the skull. The first tumor receded under treatment with roentgen rays, but others formed, and ultimately the patient died. Numerous partial fractures may be found in Paget's disease, especially along the anterior surface of the tibia. They are to be seen as transverse lines at right angles to the shaft. But in Paget's disease spontaneous fracture is rare. When it takes place the formation of callus and union may be very slow. The cortex, which early in the disease is often rarefied, owing to osteoclastic resorption, may and often does become denser, because of the excessive formation of bone subsequently laid down by osteoblasts, and the thickness of the bone also increases by subperiosteal formation. This is an important point in the differential diagnosis between osteitis deformans, osteitis fibrosa and secondary prostatic carcinoma. In the first disease the width of the skeleton is increased, and the shaft of the long bones may show much increase in weight. The presence of soft osteoid tissue leads to bending of the bones located where weight is prevalent such as the tibiae and femora and, of course, gives the well known appearance of Paget's disease in established cases. Bending may be observed also in the cervical part of the spine, and a close apposition of the occipital bone to the spinous process of the atlas may sometimes be seen. Spinal kyphosis may occur, and ankylosis of the vertebrae may follow, with resulting rigidity.

Calcification of the arteries is a common observation in Paget's disease. The femoral artery, as well as the arteries of the pelvis, often show considerable thickening.

Illustrative Cases.—Case 23.—This patient exhibited most extensive evidence of osteitis deformans. The bones of the pelvis were increased in density and showed marked striations and a typical cotton-wool appearance (fig. 1). Extensive resorption was present on the right side of the pelvis, the ilium and the femur being affected to such an extent that fracture had taken place through the neck of the right femur. Increase in the width was evident, as is often the case in Paget's disease. The shaft of the femur showed marked absorption, but an increase in the cortex was evident, and the deposition of new bone in the periosteum was plainly seen. It is interesting to note the difference in the density of the two femora, the left one showing the result of osteoblastic repair, whereas the right showed the osteoclastic condition (fig. 2).

The upper half of the tibia showed marked changes, and the skull showed extensive thickening and enlargement (fig. 3). There was also some increase in the size of the pituitary fossa, and the typical signs of Paget's disease were present.

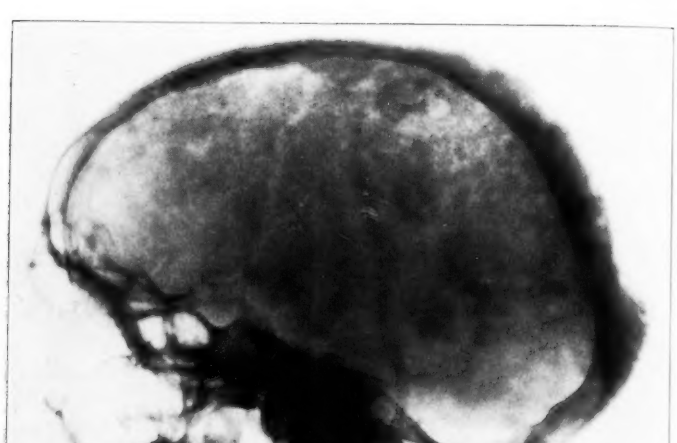

Fig. 3.—Roentgenographic appearance of the skull, showing typical changes of osteitis deformans.

Fig. 4.—Roentgenogram of the bones of the forearms, showing softening, increased density and bending of the right radius in osteitis deformans.

The skull was nearly an inch in thickness in the posterior portion. Softening of the long bones had taken place, especially of the right radius, in which definite bending was present (fig. 4). Here the medullary portion and the cortex were not differentiated, and areas of rarefaction appearing cystic were evident. The bone was increased in width, and, on the whole, a definite increase in density was

Fig. 5.—Typical cotton-wool appearance of the spine in osteitis deformans.

also to be seen in both forearms. The spine was extensively involved and showed the typical cotton-wool appearance (fig. 5).

CASE 5.—The skull of this patient exhibited definite signs of Paget's disease. No change was visible in the bones of the spine, and there was nothing diagnostic in the upper end of the tibiae. On roentgenographic examination of the skull, there was no doubt as to the diagnosis of Paget's disease. Areas of increased density by the side of patches of decalcification were present. Thickening of the calvarium and lack of differentiation of the tables were evident.

SUMMARY

1. Thirty-four cases of osteitis deformans are described, the age, sex and familial incidence being noted.

2. The mode of onset and the frequency and significance of the pain are described.

3. The types of skeletal changes are recorded, and the factors involved in their production are indicated. Pathologic fractures and sarcomatous changes are noted.

4. Spastic paraplegia is described in two cases, as are also lesser manifestations of neurologic involvement in other cases. It is concluded from present studies and from a review of the literature that neurologic changes in osteitis deformans are usually secondary to bony compression and to arteriosclerosis.

5. Two cases of psychosis are described, and the literature is reviewed. It is concluded that the occurrence of psychosis is no special feature of osteitis deformans but may be due to the concurrent arteriosclerosis.

6. The frequency of arterial degeneration and its occasional complications are observed.

7. Ophthalmologic changes are found to be dependent on bony compression or arterial degeneration. Deafness may be due to compression of the auditory nerve or labyrinth but is more usually associated with disease of the middle ear.

8. The constant occurrence of a high content of plasma phosphatase is observed, and its significance is discussed. The blood calcium and inorganic phosphates are found to approximate normal values.

9. The various etiologic theories are discussed. The syphilitic and neurotrophic theories are found to be without foundation. It is considered that the possible phases of parathyroid activity may be secondary to bony changes of unknown origin. There is insufficient evidence at present to prove that the condition is caused by disturbed function of a ductless gland, inflammation or a possible combination of these two factors.

10. The roentgenographic features of osteitis deformans are described.

PHYSICAL SIGNS AND ROENTGENOGRAPHIC FINDINGS IN LOBAR PNEUMONIA IN ADULTS

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The physical findings in lobar pneumonia are as familiar to clinicians as are the roentgenographic appearances of the lesions to the roentgenologist, but there are few recorded studies relating in any detail these two aspects of the disease. An investigation of this nature involves consistent observation on the part of the clinician and close cooperation with the roentgenologic department in order to obtain satisfactory data. The results of such a systematic study of forty cases of pneumococcus lobar pneumonia are reported in this paper.

This group of cases is obviously too small to justify any statistical treatment of the data. Furthermore, serum therapy was used in most of the type I and type II cases. However, except in those cases in which specific therapy was administered early in the disease, the clinical course was probably little altered in regard to physical signs and roentgenographic findings.

The classification of types of cases in this series with the mortality incidence is shown in table 1.

METHOD OF STUDY

Physical examinations were made once or twice daily, and the results, with other pertinent observations, were recorded on special standard charts. Practically all examinations were carried out by one of three persons familiar with the purpose of the project.[1] At times, necessarily, the thoroughness of the examination was modified by the condition of the patient, particularly in the later stages of the disease. In these few instances sufficient observations were made to detect any gross change from the previous findings. Most of the patients were examined lying in bed, access to the back being obtained by rolling the patient from side to side. This procedure gave, in general, satisfactory results, but in some instances there was sufficient distortion of physical signs to make our observations somewhat inaccurate, in that transmission of physical signs to the unaffected side gave us

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1. Dr. L. T. Coggeshall assisted in making these observations.

false evidence of apparent involvement in new areas. More recently the patients have been supported in a sitting position during the examination. If properly carried out with adequate assistance, the latter procedure rarely causes distress, and one obtains much more accurate observations.

Daily roentgenograms of the chest were made in most of the cases during the febrile period of the illness. Subsequently, roentgenograms were made at irregular intervals, depending on the course of the convalescence. A portable x-ray apparatus was generally used during the active stage of the disease. Except in rare instances the necessary manipulation for obtaining these films caused little inconvenience to the patient. Occasionally, with extremely ill patients under continuous oxygen therapy, the roentgenograms were omitted.

Histories were carefully taken in an attempt to ascertain, within a few hours, the actual onset of symptoms. However, the onset is not always abrupt, and the patients were occasionally unable to give adequate information. In these cases some arbitrary time was set at which the disease seemed definitely established. A sudden chill or onset of fever or a pleuritic pain developing abruptly without definite prodromal symptoms, when given in the history, was taken as the beginning of the illness. Such symptoms do not represent the theoretical inception of the

TABLE 1.—*Classification and Mortality Incidence in Forty Cases of Pneumococcus Lobar Pneumonia*

Type	Serum Therapy	No Serum	Recovery	Deaths
I	12	1	12	1
II	3	2	5	0
IIa	0	7	6	1
III	0	6	2	4
IV	0	9	6	3
Total	15	25	31	9

disease but indicate the generally accepted time of onset. They are sufficiently constant features to serve as a practical base line for calculation of time intervals. All measurements of time, unless otherwise stated, were calculated from such an arbitrarily established base line. Except in the early stage of the disease, when hours from onset are recorded, all time intervals between observations have been estimated to the nearest half day.

Attention has been directed particularly toward (1) the factors involved in early diagnosis; (2) correlation between the appearance of the roentgenogram and the character of the physical signs in all stages of the disease; (3) the evolution of the disease as observed by the roentgenogram, and (4) the occurrence of visceral displacement.

FACTORS IN EARLY DIAGNOSIS

The necessity of early diagnosis has become of paramount importance since the introduction of specific serum therapy. With this in mind, a presumptive diagnosis of lobar pneumonia should be made in any patient with a history of an acute onset of infection with signs or symptoms referable to the pulmonary system. If, in addition, rusty or blood-tinged sputum containing a predominance of pneumococci is present, the diagnosis is practically certain. The latter finding is not always present in the early stage, and consequently one must utilize all other

available evidence. The white cell count is often of distinct value, for most patients, even at the beginning of the infection, have a marked leukocytosis. A few, however, do not show this reaction.

In table 2 are tabulated the various objective findings and pulmonary symptoms seen within thirty hours after onset. The pneumococci were isolated from the sputum, blood culture or fluid obtained by puncture of the lung, and, in many instances, from at least two of these sources. The column under roentgenographic evidence designates merely presence or absence of roentgenographic signs of a pulmonary lesion and not the extent of the pathologic process. The physical signs, which were extremely variable, are recorded without designation of their

TABLE 2.—*Signs and Symptoms in Early Stage of Pneumonia*

	Type of Pneumococcus	Time After Onset, Hrs.	Physical Signs	Roentgenographic Evidence	Symptoms	White Blood Cells
G. F.	II	5	None	+	Pleural pain	21,000
A. M.	II	8	Dulness	+	Pleural pain	10,000
E. C.	IV	13	Dulness; bronchial breathing	+	Pleural pain; dyspnea; cough	13,000
R. H.	I	15	None	+	Rusty sputum; cough	22,000
R. O.	I	19	Dulness	0	Pleural pain	34,000
J. A.	I	21	Bronchial breathing	+	Dyspnea	28,000
E. M.	I	21	None	+	Pleural pain; cough	28,000
C. H.	III	22	Dulness; diminished breath sounds	+	Pleural pain; cough	22,000
F. S.	II	23	Dulness; bronchovesicular breathing	+	Dyspnea	18,000
R. E.	IIa	24	Dulness	+	Pleural pain; bloody sputum	23,000
L. P.	IIa	24	Dulness; bronchial breathing	+	Rusty sputum	28,000
G. H.	I	25	Dulness; diminished breath sounds	+	Cough; dyspnea; rusty sputum	13,400
H. C.	III	29	Dulness; bronchial breathing	+	Pleural pain	6,400
A. L.	I	30	Dulness	+	None	28,000

intensity or extent. In several instances the signs were so minimal that they would easily have been discounted if lobar pneumonia had not been strongly suspected. As will be pointed out later, the degree of intensity of the physical signs, at this stage, often gave no indication of the extent of the lesion as disclosed in the roentgenogram.

In all cases there were sufficient signs or symptoms relating to the pulmonary system to warrant a presumptive diagnosis of lobar pneumonia. About one fourth of these patients had sputum containing pneumococci when first seen. The leukocytosis was generally definite. One patient, A. M.$_{II}$, however, who went through a severe illness despite early serum therapy, never had a white cell count above 13,000. E. C.$_{IV}$, who exhibited a very mild disease, did not exceed the initial count. G. H.$_{I}$ had a white cell count of 34,000 in the second twenty-four hours. H. C.$_{III}$, with an initial count of 6,400, was at the peak of the disease at

twenty-nine hours with full consolidation of the left lower lobe and partial consolidation of the right lower lobe, and resolution began at three days. The highest count was 10,000 during this time.

Physical signs in the early stage were variable. Detectable dulness was present in ten of the fourteen patients, though in several this was extremely slight. Diminished or increased intensity of breath sounds, with or without râles, occurred less often than dulness, namely, in six of the fourteen cases. In the early period the physical signs rarely involve the area of a whole lobe, so from the point of view of diagnosis they serve only to localize the infectious process in the chest as do the symptoms of pleurisy, cough, sputum or dyspnea.

In hospitals the roentgenogram affords considerable aid in early diagnosis, as is well illustrated in table 2. Of this series, only one patient, R. $O._1$, first seen nineteen hours after the initial symptoms, failed to show any shadow in the roentgenogram. However, the character of the onset of the disease, the leukocytosis, pleuritic pain and dulness, which were quite definite, sufficed to warrant a presumptive diagnosis of early lobar pneumonia. Later, the classic signs of consolidation of the entire lower right lobe developed, but the roentgenograms never showed more than faint graying in this region, even though the films were technically satisfactory.

Twenty of the forty patients were first seen forty-eight hours or less after the beginning of the disease. None of those examined after twenty-four hours failed to show a definite lesion in the roentgenograms, although even at this stage physical signs were occasionally absent or minimal, and difficult to detect. One should question seriously a diagnosis of lobar pneumonia in any case in which it is suspected, which, forty-eight hours after onset, fails to show some lesion in the roentgenogram. Only one patient in the series (R. $B._{IIa}$, table 4) afforded a possible exception to the foregoing statement. This patient was first seen four and one-half days after the initial symptoms of a sudden chill and temperature. Rusty sputum had appeared the day before entry to the hospital. There were no signs suggesting consolidation at the first examination, but crepitant râles were heard throughout the region of the entire lower right lobe. The roentgenogram at that time showed only increased markings in the upper portion of the lower right lobe. Subsequently, signs of consolidation developed over the entire posterior portion of the chest except at the extreme apex and base, with increased density in the same area, as shown by the roentgenogram. It would seem that a diagnosis of lobar pneumonia on the basis of roentgenographic or physical signs would have been difficult in the first forty-eight hours.

COMPARISON OF PHYSICAL SIGNS OF CONSOLIDATION AND ROENTGENOGRAPHIC APPEARANCE OF THE LESION AT VARIOUS STAGES OF THE DISEASE

The Developing Lesion.—Until the consolidation reached its maximum, the roentgenogram was found to be much more accurate than the physical signs in disclosing the extent and character of the lesion. The almost invariable presence of an abnormal density in the roentgenogram within twenty-four or forty-eight hours after onset has been pointed out. Comparable manifestations of the lesion as indicated by physical signs occurred less consistently during this early period. Although

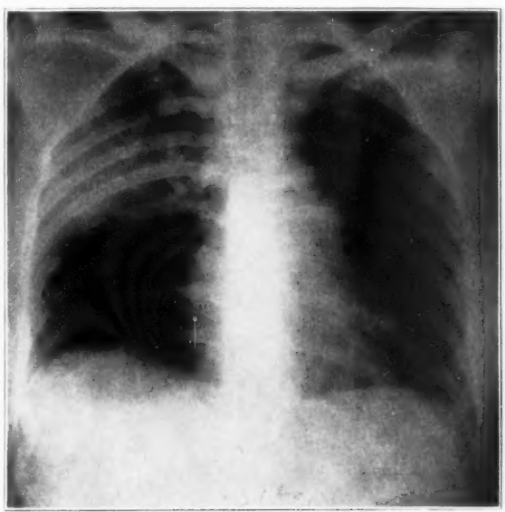

Fig. 1 (E. $M._1$).—Roentgenogram taken twenty-one hours after onset. No abnormal physical signs were detected. Note that elevation of the diaphragm was present at this early stage.

physical signs of consolidation were generally present, they tended to be quite minimal and rarely indicated as extensive a lesion as was shown by the roentgenogram.

This is illustrated by the roentgenograms (figs. 1 to 4) of the following patients observed within the first twenty-four hours after the onset of the disease (see tables 2 and 3 for other data).

In E. $M._1$ (fig. 1) there was the most striking divergence between the degree and the extent of roentgenographic density and physical signs. This obvious lesion in the upper right lobe gave no definite physical signs of consolidation over the involved area. In R. $H._1$ (fig.2)

no abnormal physical signs were detected until fifty-seven hours after the onset of the disease, when the lesion in the roentgenogram was quite marked. Physical examination of G. F.-II (fig. 3) disclosed no evidence of consolidation. The lesion in F. S.-II (fig. 4), which gave a conclusive roentgenographic shadow, caused such meager physical signs that their significance was in doubt until the roentgenogram was seen.

In contrast to these findings, there were three cases in which the evidence of consolidation by physical signs was much more pronounced than in the roentgenogram. In these cases only a faint graying of the affected area of the lung was seen in the daily roentgenograms, although the physical signs were those of frank consolidation. This lack of characteristic density could not be attributed entirely to faulty roentgeno-

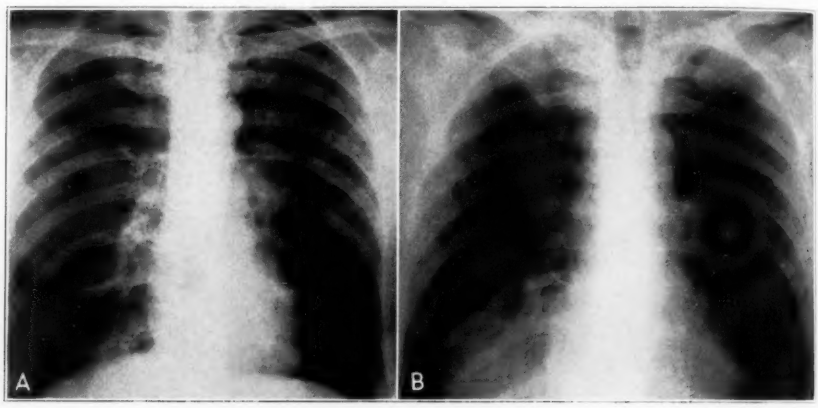

Fig. 2 (R. H.-I).—*A*, roentgenogram taken fifteen hours after onset. A beginning lesion is seen along the right border of the heart. There were no physical signs of consolidation. *B*, appearance thirty-eight hours after onset. No physical signs of consolidation were detected.

grams, because the findings were consistent throughout the individual series despite variations in the technic of exposure.

Time of Maximum Consolidation.—By the time a lesion had progressed to its maximum consolidation, the divergence between the roentgenographic and the physical signs was no longer so apparent. In most cases the consolidation, when fully developed, was equally well demonstrated by either method.

In tables 3 and 4, the time of maximum consolidation, onset of resolution and rate of clearing, as disclosed by the two methods of examination, are tabulated. The time of maximum consolidation has been taken as the interval between the onset of the disease and the point of time at which the greatest intensity and extent of physical signs or roentgeno-

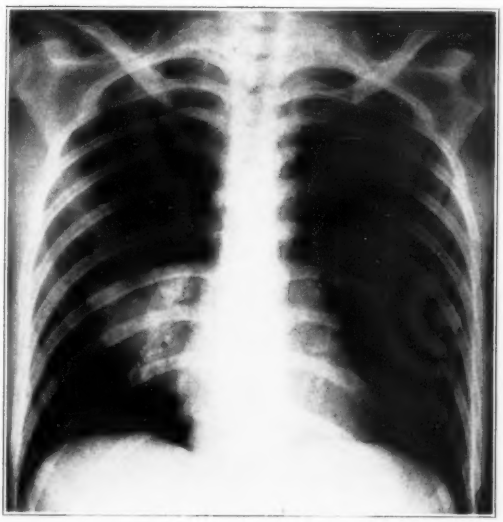

Fig 3 (G. F.11).—Roentgenogram taken five hours after onset. No physical signs of consolidation were detected.

Fig. 4 (F. S.11).—Roentgenogram taken twenty-three hours after onset. A small area of slight dulness and faint bronchovesicular breathing were detected at the inferior angle of the right scapula.

graphic density were found. Maximum extent of the lesion as shown by roentgenographic or physical examination does not necessarily correspond to the time of maximum intensity of density in the roentgenograms or of signs of consolidation. For example, it was often noticed

TABLE 3.—*Data on Patients Treated with Serum Who Recovered*

	Type of Pneumococcus	Time of Maximum Consolidation		Day of Onset of Resolution		Day of Crisis or Lysis	Time of Beginning Serum Treatment	Duration of Resolution in Days*		Lobes Involved
		X-Ray	P. E.	X-Ray	P. E.			X-Ray	P. E.	
G. F.	II	5 hrs.	33 hrs.	5	2	2-4	13 hrs.	8	3	One‡
F. S.	II	23 hrs.	23 hrs.	3½	2½	2	25 hrs.	9+†	8	One‡
E. M.	I	21 hrs.	22 hrs.	4½	3½	2	23 hrs.	7	7	One
R. H.	I	2½ days	3½ days	5½	5½	4-6	36 hrs.	..	17	One
G. H.	I	3 days	3 days	5	9	3	48 hrs.	12	7	One
J. A.	I	3½ days	3½ days	5½	5½	4	40 hrs.	13	13+	One
A. M.	I	3½ days	4½ days	6½	6½	7	72 hrs.	2	20+	One
M. T.	I	3 days	3 days	6	6	4-6	48 hrs.	30	30	One
R. O.	I	3 days	4 days	6	6	4-6	36 hrs.	..	17	One
J. L.	I	3½ days	3½ days	4½	4½	7	67 hrs.	41+	33+	Two§
A. M.	II	3 days	3 days	6	5	5	36 hrs.	6+	18+	Two§
M. E.	I	6 days	6 days	7	7	6	6 days	15	..	Two
McC.	I	6 days	6 days	9	9	8-12	6 days	77	77+	Two

* From onset of resolution to the time of disappearance of the lesion.
† Remnants of physical signs or roentgenographic density still remaining at the last examination. (See text.)
‡ Considerably less than one lobe involved.
§ More than one but less than two lobes involved.
X-Ray and P. E. indicate roentgenographic and physical examination, respectively, in this and the following table.

TABLE 4.—*Data on Untreated Patients Who Recovered*

	Type of Pneumococcus	Time of Maximum Consolidation		Day of Onset of Resolution		Day of Crisis or Lysis	Duration of Resolution in Days*		Lobes Involved
		X-Ray	P. E.	X-Ray	P. E.		X-Ray	P. E.	
L. P.	IIa	1 day	1½ days	3	4	2-6	7+†	2	One
E. C.	IV	30 hrs.	30 hrs.	2½	2½	2-6	6+	8+	One
B. G.	IIa	3 days	3 days	6	6	5	8+	8+	One
M. K.	IV	2 days	4 days	6	6	4-14	..	10	One
F. V.	IV	4 days	4½ days	7	6	8-10	18	18	One
L. B.	IIa	5 days	5 days	8	8	7	..	14+	One
A. C.	III	6 days	6 days	7	7	4-6	12	12	One
A. L.	I	6 days	5 days	7	7	5	20	15+	One
R. B.	IIa	6 days	6 days	7	7	8	10+	8	One
F. T.	IV	.....	.....	13	12	7	26	35+	One
H. C.	III	29 hrs.	29 hrs.	3	3	2-9	11+	16+	Two‡
M. R.	IIa	6 days	7 days	8	8	5-7	13+	15	Two‡
K. H.	III	4 days	5 days	7	7	7	12	12	Two
M. M.	II	.....	.....	10	10	8-10	8+	8+	Two
R. E.	IIa	6 days	6 days	8	8	7	11+	8	Three
W. S.	IV	5 days	6 days	6	7	7-12	15+	15+	Three

* From onset of resolution to the time of disappearance of the lesion.
† Remnants of physical signs or roentgenographic density still remaining at the last examination. (See text.)
‡ More than one but less than two lobes involved.

in pneumonia of one lobe that the entire lobe would be involved within forty-eight hours, but the maximum intensity of the physical signs or of the roentgenographic density would not be apparent until twenty-four hours later. Hence the time of maximum consolidation in such a case would be recorded as three days.

On the basis of tabulating the time of maximum consolidation, there is noted in tables 3 and 4 significant uniformity between the development of maximum physical signs and the roentgenographic density. Up to this point the extent and intensity of physical signs were usually considerably in arrears of the apparent involvement in the roentgenogram. Maximum physical signs occasionally did not appear until after maximum density, as shown by the roentgenogram developed, and the opposite situation was also noted. Usually, however, there was a fairly close uniformity in this stage of the disease as detected by these two methods of examination.

We found that of the several signs of consolidation, dulness to percussion usually gave the most accurate evidence of the extent of the lesion as compared with that shown in the roentgenogram. Bronchial breathing or bronchophony frequently conformed to the extent of the area of dulness, but much less often exceeded it than fell short of it.

Onset of Resolution.—Diminution in extent or intensity of physical signs or roentgenographic density was employed as the criterion of beginning resolution. It is seen in tables 3 and 4 that there was a remarkably close correspondence between roentgenographic and physical examination in indicating the inception of this stage of the disease. Roentgenographic evidence of resolution occasionally preceded, and in a few instances followed the physical signs denoting clearing of the lesion. In the majority of cases this stage of the disease was recognized equally well by either method of examination.[2]

EVOLUTION OF THE DISEASE AS DISCLOSED BY ROENTGENOGRAMS

Sites of Foci of the Pneumonic Lesion.—The original focus of infection, as well as the foci of later areas of involvement, was observed in various areas of the nonstereoscopic pulmonic field. Most of the original foci appeared near the region of the hilus. In figures 4 and 5 the lesions occupied more central portions of the lobe. The focus of spread in the right side of the chest in figure 5 presented an unusual appearance and, because of its sharply circumscribed borders, resembled a carcinomatous metastasis. This lesion subsequently spread laterally and, at the height of its development, was a triangular area of density with its apex at the hilus and its base at the periphery. Figure 6 shows the pneumonic process originating in the peripheral portion of the lung and spreading toward the hilus.

2. Occasionally one can predict the beginning of resolution by physical signs before the criterion mentioned is established, by the advent of coarse, moist râles over the consolidated area. However, this is not an entirely dependable sign, for it does not occur with regularity and may appear without definite relation to resolution.

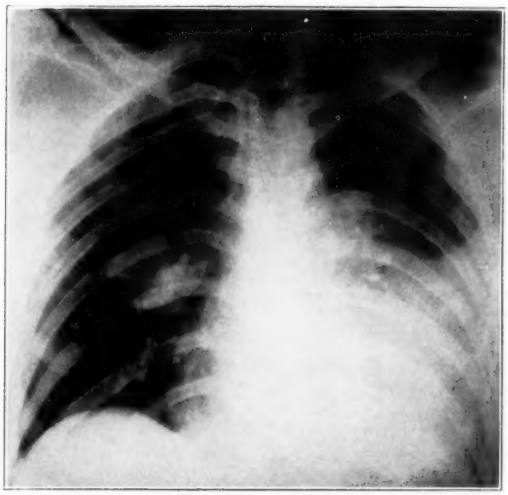

Fig. 5 (R. E.$_{11a}$).—Roentgenogram taken three days after onset. No abnormal physical signs were found in the region of the lesion in the right side of the chest.

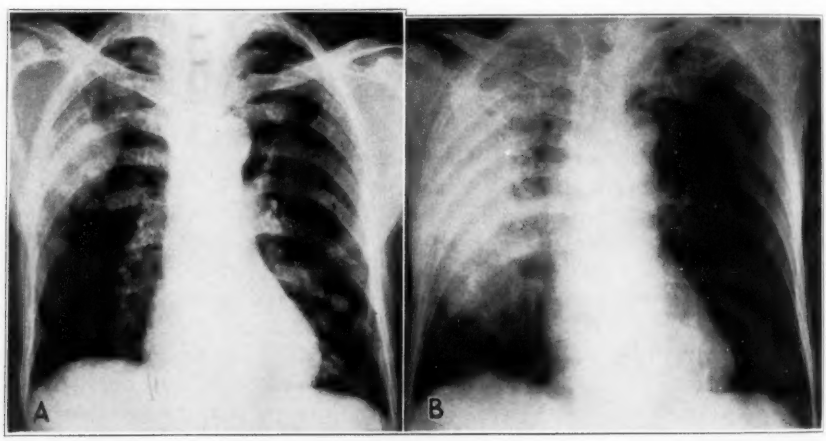

Fig. 6 (McC.$_{1}$).—*A*, roentgenogram taken thirty-six hours after onset. Physical examination was not made at this time. *B*, appearance six days after onset. Classic signs of consolidation were present over the upper third of the anterior right side of the chest and the upper two thirds of the posterior right side of the chest.

Rate of Development of Consolidation.—It is often stated that the maximum consolidation occurs in lobar pneumonia at about forty-eight hours. Our findings as summarized in tables 3 and 4 did not confirm this opinion. The cases have been listed in sequence according to the amount of pulmonary tissue involved at the height of the disease. Of necessity, this was an estimation, because frequently it was impossible to be certain that entire lobes, or exactly which lobes, were involved, particularly in the right side of the chest. The classification is sufficiently accurate, at least, to show the lack of uniformity in the rate of consolidation. This variation occurred quite independently of the type of pneumococcus producing the disease.

It is apparent from the data presented that the time required for maximum involvement of either a single lobe or several lobes as detected by either roentgenographic or physical signs was, in the majority of instances, three days or more. In six of the twenty-seven tabulated cases maximum consolidation occurred in thirty hours or less. Serum treatment was given in three of these cases. In two patients, G. F.$_{II}$ and F. S.$_{II}$ (table 3 and figs. 3 and 4), the pneumonic process was apparently arrested and did not involve a whole lobe. In the three untreated patients in this group, the most rapid maximum involvement of an entire lobe occurred within twenty-four hours (L.P.$_{IIa}$, table 4). H. C.$_{III}$ (table 4) showed involvement of one lower lobe and a small area of consolidation in the other lower lobe twenty-nine hours after the onset of the disease. With the exception of these six cases and one other which reached the height of the disease within forty-eight hours, maximum consolidation did not occur until three days or more after the onset of the disease. With multilobed lesions, the day of maximum involvement generally appeared later than when only a single lobe was affected, since the process usually spread from one lobe to another.

Rate of Resolution.—The rate of resolution was likewise found to vary greatly. The figures given on the rate of disappearance of the lesion (tables 3 and 4) were calculated from the day of beginning resolution, as determined by the roentgenogram and by physical examination, respectively, to the time of disappearance of evidence of consolidation. Restitution to normal, roentgenologically, was taken as the time at which there was no remaining evidence of consolidation, although usually accentuation of the bronchovascular markings persisted in the previously affected areas. If any abnormal physical signs or roentgenographic density, however slight, was present on the last examination, a plus sign was used to designate its persistence. The data on the duration of resolution are incomplete in the series, because many of the patients were discharged from the hospital before the lesion had entirely cleared. Furthermore, roentgenograms were taken less frequently during this

stage. In some instances small pleural effusions appeared during convalescence and obscured the roentgenogram as well as disturbed the physical signs of consolidation.

A rough analysis of the data shows that in seven of the cases physical signs of consolidation disappeared about the same time as the roentgenographic evidence. In four cases the roentgenograms appeared to be normal before the signs had receded, and in six instances the reverse situation was noted. In the rest of the cases no adequate comparison could be made because of incomplete observations.

It is shown by the data, presented in tables 3 and 4, that the rate of resolution was quite variable. Weeks or months may be required.

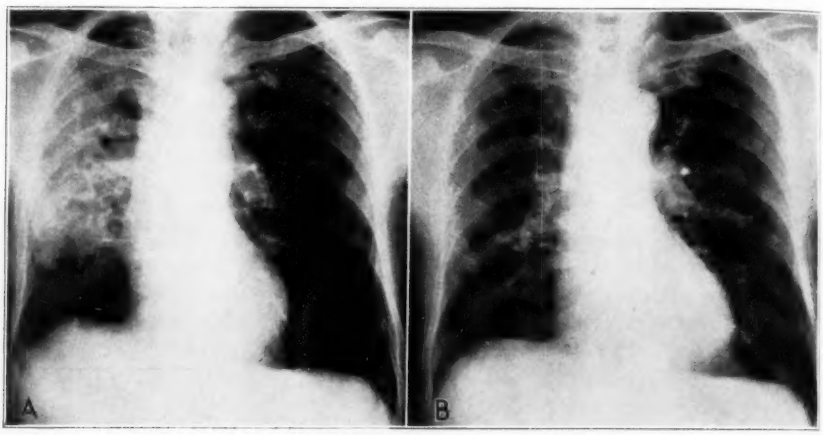

Fig. 7 (McC$_1$).—*A*, roentgenogram taken twenty-nine days after the onset of the disease, twenty days after beginning resolution. Physical signs of consolidation were decreasing slowly. Note the deviation of the trachea and elevation of the right side of the diaphragm. *B*, appearance eighty-five days after onset and seventy-six days after beginning resolution. Slight dulness was present over the right scapular area. The roentgenographic appearance is now practically normal.

One patient, McC$_1$ (table 3, figs. 6 and 7), was observed for seventy-seven days throughout a period of exceedingly slow resolution. The last roentgenogram (fig. 7 *B*) showed a practically normal appearance, though the film taken thirty-eight days before this was far from normal. Some dulness still remained at the time of the last examination.

In this series there was no uniformity in persistence of any particular sign of consolidation. Dulness was less likely to remain than some alteration in the transmission of voice or breath sound. Increased whispered voice was often the last abnormal sign to disappear.

Sante [3] stated that resolution, as shown by the roentgenogram, should be complete in two weeks in any normal convalescence. It is probably true that most cases have practically cleared up at this time, but many have not, and resolution continues at a slower rate with eventual complete recovery.

Sequence of Resolution.—It was found impossible to make a definite statement in regard to the sequence of clearing of a single lobe. Whereas spread in one lobe occurred generally as an even uniform involvement, the clearing process took place in a distinctly patchy manner. It was practically impossible to detect any distinct difference in the rate of resolution of any one portion of the lobe, except that the hilar densities in general subsided more slowly than the main peripheral areas.

In cases showing involvement of more than one lobe, several types of resolution were observed. In several instances of multilobed involvement in which the focus of spread had not advanced to complete involvement of an entire lobe, the later area of infiltration cleared more rapidly than the older process. This may be more apparent than real because of the lesser amount of tissue involved in the later focus. In other cases, however, in which two or more lobes were involved in sequence with several days' difference in the time of maximum consolidation, the signs of beginning resolution appeared in all areas simultaneously. In some instances the first lobe involved gave the first evidence of clearing. Two cases with lesions of multiple lobes showed resolution proceeding in the earliest area of involvement, while actual spread was taking place into new foci. In one of these cases the pneumonia was a type IV; in the other, a type II. Roentgenograms of one of these patients, K. V_{IV}, are shown in figure 8. The original lesion began in the lower right lobe, then gradually spread upward until the entire right lung had been consolidated. Before this process was completed, resolution had taken place in the area first infected.

Unfortunately, there were too few cases in the series suitable for adequate study of these phenomena of resolution to make possible any statement as to the factors concerned. Usually resolution appeared first in the older lesion, although in certain instances the more recently involved areas began to clear simultaneously or even before the older lesion. Our knowledge of the mechanisms of resolution is inadequate to explain these different types of reaction.

OCCURRENCE OF VISCERAL DISPLACEMENT

Elevation of the Diaphragm.—In twenty-nine of the forty cases here reported the diaphragm was well visualized in the roentgenogram at some time during the active stage of the disease. In eighteen cases

3. Sante, L. R.: The Chest, Ann. Roentgenol. **11**:203, 1930.

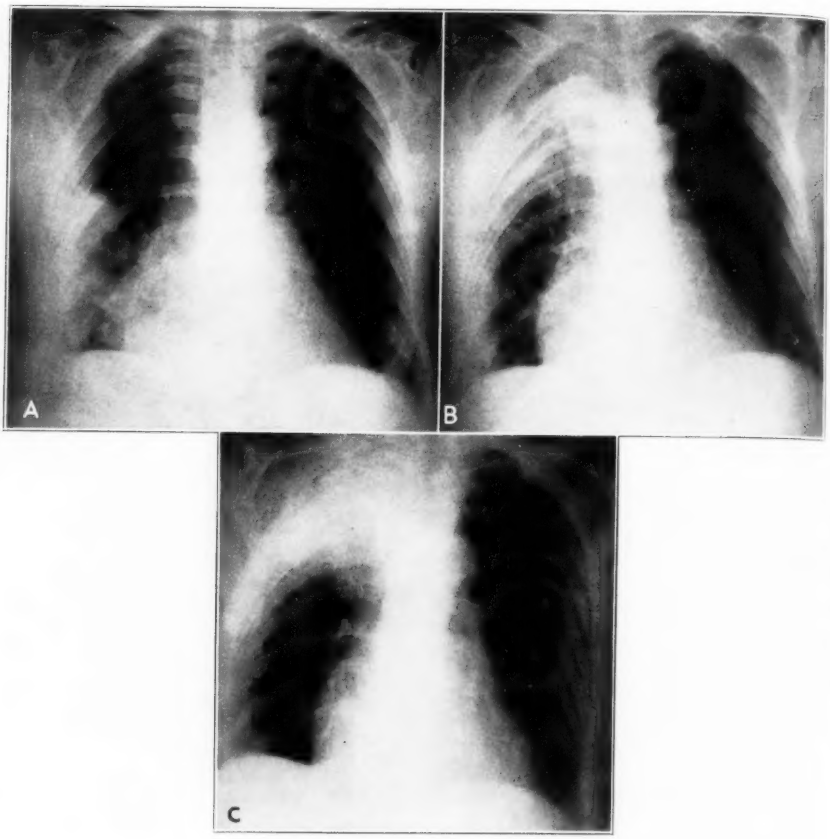

Fig. 8 (K. $V._{IV}$).—*A*, roentgenogram taken five days after onset. The first roentgenogram taken three days after onset showed maximum density near the cardiac shadow. Some clearing in this region is already apparent. There was no evidence of resolution by physical examination. *B*, appearance seven days after onset. The lesion is spreading upward while clearing progresses in the lower areas. The physical signs of consolidation have extended upward. There was an increase in moist râles at the base of the right lung at this time, suggesting resolution. *C*, appearance eight days after onset. Further spread and resolution have occurred. The physical signs of consolidation had greatly diminished at the base and had spread upward to include the apex.

there was definite elevation of the leaf of the diaphragm on the affected side. Eleven did not show this change, but in most of these cases the outline of the diaphragm was obliterated by a small amount of fluid or by dense consolidation, so that one cannot state whether or not there was elevation later in the disease.

Several of the cases in this series were studied with the double exposure technic described by Jung and Van Allen,[4] in which the film is exposed at both maximum inspiration and maximum expiration. By this technic the maximum excursion of the two sides of the diaphragm may thus be compared in the same film. These cases were reported in a separate paper.[5] All of them showed elevation or diminished excursion of the diaghragm on the affected side. In one case in this group a roentgenogram made during deep inspiration with the usual technic failed to show elevation of the diaphragm, but with the double exposure technic the roentgenogram showed definite diminution in the extent of the excursion of the diaphragm on the side of the lesion. It would appear from this observation that alteration in the relationship of the two sides of the diaphragm in some instances would not be apparent in the films taken at the moment of maximum inspiration.

All grades of elevation of the diaphragm from slight to marked were noted in the series. Elevation was rarely detected by physical signs. In certain instances the diaphragm resumed its normal position within a few days after resolution began, but in others the elevation persisted even after the lesion had apparently resolved.

Displacement of the Mediastinum.—Displacement of the mediastinal structures was not a prominent feature in the roentgenographic findings in this series. Detection of slight changes in the position of the mediastinum was rendered difficult because many of the films were made with a portable x-ray machine at the bedside, with the result that often the sagittal plane of the chest was not perpendicular.[6]

However, taking this factor into consideration, there were three cases in which there was slight but definite displacement of the mediastinum toward the affected side during the acute stage of the disease. In one other case, not included in the series of forty, there was marked displacement when the patient was first observed, forty-eight hours after onset. This case, in contrast to the other three, presented the classic

4. Jung, T. S., and Van Allen, C. M.: A Method of Recording Respiratory Movements in a Single Roentgenogram, Nat. M. J. China **17**:194, 1931.

5. Wu, Ching: Visceral Displacement in Pneumonia, Radiology **19**:215, 1932.

6. The ideal roentgenologic examination for demonstration of this phenomenon would consist of stereoscopic films and fluoroscopic observation. Facilities for stereoscopic filming of bedridden patients are now available and will be reported presently by others. They had not been developed at the time this work was done.

signs of atelectasis [7] and a degree of mediastinal shift seen in cases of "massive collapse." There were diminished to absent breath sounds over the entire left anterior portion of the chest and frank signs of consolidation at the base posteriorly. The displacement of the heart to the left was detected by physical examination and was clearly seen in the roentgenogram. After twenty-four hours the signs had changed markedly. The heart had returned to almost normal position, and there was good aeration of the anterior portion of the chest. Posteriorly, the signs of consolidation had greatly diminished. Unfortunately this patient had a moderately enlarged heart which obscured part of the lower left portion of the chest, so that no good evidence of consolidation was seen in the roentgenogram, though the physical signs were quite definite. Atypical type II pneumococci were recovered from the sputum. Although there was undoubtedly true collapse present, as well as some pneumonic lesion, we are not warranted in submitting this case as a typical example of lobar pneumonia. One must say, however, that collapse of the lung of this type may occur in rare instances of pneumococcus pneumonia.

In four cases there was definite displacement of the mediastinal structures during the stage of resolution. The most striking patient in the entire series was McC.1 (figs. 6 and 7, table 4), who was observed throughout a period of protracted resolution. Figure 6 *A* shows a lesion which began at the periphery and reached its maximum development six days (fig. 6 *B*) after the onset of the disease. By this time there was slight displacement of the trachea toward the lesion. Resolution began on the ninth day. Figure 7 *A* was made twenty-nine days after onset, or twenty days after resolution began. At this time maximum visceral displacement was apparent. Also, there was marked diminution in the area of the right pulmonic field in comparison with that of the left pulmonic field. The difference in the two sides was probably the result of diminished expansion of the right lung, combined with compensatory emphysema of the left lung. Figure 7 *B*, made eighty-six days after the onset of the disease and seventy-seven days after resolution began, shows almost complete restitution to normal. The diaphragm was still slightly elevated, but the trachea had resumed its normal position, and there had been a considerable increase in the area of the right pulmonic field. There were still some abnormal physical signs present, but these were very slight. This was our last observation on this patient. At no time were there any of the usual physical signs of atelectasis.

7. The term "atelectasis" is used here in the sense of "airlessness" due to collapse of the lung.

COMMENT

The data presented in this paper are part of a systematic attempt to correlate certain clinical, immunologic, bacteriologic and pathologic features of pneumococcus pneumonia. Even in this small series the extreme variability of the reaction of individual hosts to the same type of pneumococcus was apparent. The classic picture may result from infection with any type. Pneumonia due to the group IV pneumococcus seemed to present the greatest variation; the disease caused by types I and II, the least. In the studies on experimental pneumonia in dogs reported by Terrell, Robertson and Coggeshall,[8] in which dosage and type were controlled, this same variability was apparent.

We attempted to correlate the degree of leukocytosis with the intensity of the roentgenographic shadow and the severity of the disease. In this respect, also, there was great divergence of findings. There were instances of marked density with relatively low white blood cell counts as well as the opposite situation. In general, of course, the severe cases had the more marked leukocytosis, but the degree of white cell reaction certainly showed no constant relation to the type of pneumococcus causing the disease. Likewise, the febrile reaction of the patient showed no consistent relationship to the type of pneumococcus.

From a study of the data in tables 3 and 4, one is impressed with the considerable variability in the time relationship of resolution to crisis. The onset of resolution may precede, occur simultaneously with, or follow crisis. Usually it follows crisis. Furthermore, resolution may be proceeding in one area while spread into other regions is occurring and the toxic symptoms of the disease are persisting. Thus the abrupt and the more prolonged fall of temperature with the concomitant decrease of toxic symptoms, which are called crisis and lysis, respectively, are not directly related to the phenomena of resolution, as Cole has pointed out.[9]

A point of practical interest brought out by this study was the assistance which may be derived from the roentgenogram in early diagnosis. In a number of instances the appearance of the roentgenogram substantiated the presumptive diagnosis, so that serum therapy was started before a definite etiologic diagnosis was made. It would be incorrect to say in general that the appearance of density in the roentgenogram in the early stage is "characteristic" of lobar pneumonia except in consideration of the history. The rapid development of the density, when its probable age is known, and its visual localization to

8. Terrell, E. E.; Robertson, O. H., and Coggeshall, L. T.: Experimental Pneumococcus Lobar Pneumonia in the Dog: I. Method of Production and Course of the Disease, J. Clin. Investigation **12**:393, 1933.

9. Cole, Rufus: Acute Lobar Pneumonia, in Nelson Loose-Leaf Medicine, New York, T. Nelson & Sons, 1920, vol. 1, p. 228.

a single focus in any one lobe serve to differentiate it from most other acute pulmonary infections.

Likewise, as has been frequently pointed out by roentgenologists, the resolving lesion may present many bizarre features. Characteristically the clearing lesion gives a patchy shadow in contrast to the even density of a developing lesion, but at times it may simulate perfectly single or multiple abscesses of the lung, or more often widespread tuberculous lesions. In a single film one could certainly not dismiss either diagnosis. Rarely, however, does such an appearance persist sufficiently long to confuse the diagnosis. A large, apparent abscess with thick capsule will disappear in several days, and, similarly, the supposed tuberculous lesion will melt away rapidly.

There is considerable confusion in the literature concerning the locus of origin of the lesion in lobar pneumonia as detected in the roentgenogram. Most writers tend to stress the relationship to the hilus. Though this perhaps is the most frequent site of the original focus, as disclosed by the nonstereoscopic roentgenogram, the lesion may occur in other areas of the pulmonic field. There are naturally few observations made on the site of the initial focus besides those made by roentgenograms. Figures 4 and 5, shown here as examples of central foci apparently not originating from the hilus or related to the lateral periphery, admittedly do not offer conclusive evidence of separation from the pleural surfaces. Undoubted evidence of a central focus unrelated to the surface of the lung or to the hilus can be obtained only at autopsy. Assmann [10] reported a case in which spread occurred from the upper right lobe to the central portion of the left lung. The latter lesion was only disclosed in a roentgenogram of the lungs after death and was corroborated by the findings at autopsy. As Mason [11] stated, no conclusive evidence has so far been produced to show that the pneumococcic lesion may occur in the center of a lobe remote from the pleural surfaces. Only by autopsy will this point be settled. The case mentioned by Assmann [10] was not reported in detail, and from his statements one cannot be certain that the lesion did not have any connection with the interlobar pleural surfaces.

The peripheral origin of a pneumonic lesion is not infrequently observed. Two examples occurred in this series; one was the original focus, and the other, the site of a later area of spread. Mason [11] made the same observation in children. In experimental lobar pneumonia in dogs, Terrell, Robertson and Coggeshall [8] produced the initial lesion by implantation of pneumococci in the periphery of the lung. Blake and

10. Assmann, Hubert: Klinische Röntgendiagnostik der inneren Erkrankungen, ed. 4, Leipzig, F. C. W. Vogel, 1929, p. 265.

11. Mason, H. H.: Lobar Pneumonia in Childhood, Am. J. Dis. Child. **11**:188 (March) 1916.

Cecil,[12] with a different technic, localized the initial focus in the hilar region of monkeys.

We have been particularly interested in studying these cases in attempting to detect evidence of atelectasis or collapse in lobar pneumonia. Coryllos and Birnbaum [13] believe this to be an essential feature in the disease. Except in one instance described in detail, we failed to detect evidence of true atelectasis in any case. This case, as was stated, could not be classed by any criteria as a typical lobar pneumonia. Of the cases seen early in the disease, i. e., within thirty hours of onset, none gave any evidence of this condition. Shift of the mediastinum does occur, but in no case in this series did it approach the degree found in massive atelectasis as diagnosed by clinical or roentgenographic signs. One must acknowledge, however, that the clinical diagnosis of this condition can be made only when considerable collapse is present. Pneumonia in children and the experimental disease in dogs unquestionably show this displacement of the mediastinum clearly in a much higher percentage of cases. However, it does not follow that the displacement is due primarily to actual collapse of a portion of the lung, though to some degree this may be a factor. The observations of Robertson, Coggeshall and Terrell [14] on the pathologic changes in experimental pneumonia are significant in that they failed to show any evidence of plugging of the bronchi, which is postulated as a necessary precursor to collapse of the lung in cases showing a definite shift of the mediastinum.

We feel that the degree of visceral displacement usually encountered in lobar pneumonia can be adequately accounted for on the basis of the experimental studies of Van Allen and Wu.[15] They demonstrated an increase in the elastic tension of the dog's lung in experimental pneumonia in both the preconsolidative and postconsolidative stages. The increased tension presumably occurs as a result of the thickening of the alveolar and lobular septums which is caused by dilated capillaries and interstitial inflammatory fluids and cells. This results in diminished expansibility of the lung, so that at full inspiration the inflamed tissue fails to expand to its usual volume. During the consolidated stage, the lung is, of course, fixed and neither expands nor contracts with respiratory movements. Under these conditions some adjustment of the pulmonary environs must take place in order to maintain the balance

12. Blake, F. G., and Cecil, R. L.: Studies in Experimental Pneumonia: II. Pathology and Pathogenesis of Pneumococcus Lobar Pneumonia in Monkeys, J. Exper. Med. **31**:445, 1920.

13. Coryllos, P. N., and Birnbaum, G. L.: Lobar Pneumonia, Arch. Surg. **18**:190 (Jan.) 1929.

14. Robertson, O. H.; Coggeshall, L. T., and Terrell, E. E.: Experimental Pneumococcus Lobar Pneumonia in the Dog: III. Pathogenesis, J. Clin. Investigation **12**:467, 1933.

15. Van Allen, C. M., and Wu, Ching: Increased Elastic Tension of the Lung in Experimental Pneumonia, J. Clin. Investigation **11**:589, 1932.

of intrapulmonary pressure. Thus, to compensate for this diminution in, or lack of, expansibility of the pneumonic lung, visceral displacement may occur.

In most cases of pneumonia in adults visceral displacement cannot be demonstrated clinically and may be apparent only in the roentgenograms taken at maximum inspiration. It is usually manifested only by alteration in the excursion or position of the diaphragm. In our studies an unmistakable shift of the mediastinum was an unusual finding. With the development of facilities for fluoroscopy and for obtaining stereoscopic films of patients with pneumonia, it is probable that more adults would show slight degrees of mediastinal shift than we have indisputably demonstrated in this series. Children and dogs both have much more mobile mediastinal structures and consequently more often show definite displacement of the mediastinum.

SUMMARY

Forty cases of pneumococcus lobar pneumonia were studied by means of serial daily roentgenograms and physical examinations. A comparison was made between these two methods of examination at various stages of the disease. The roentgenogram was shown to be superior to physical signs in detecting the early lesion and in disclosing the extent of the process while the consolidation was developing. At the stage of maximum consolidation, however, both methods of examination were, in general, equally informative. Evidence of the onset of resolution as detected by the roentgenogram and by physical signs appeared simultaneously in most cases.

Various phases of the evolution of the disease were studied in the serial roentgenograms. The rate of consolidation of lesions of a single lobe varied from one to six days. Maximum consolidation in the majority of cases did not occur until at least three days after the onset of the disease. The sequence of resolution in areas of consolidation of different ages (i. e., in different lobes) was quite variable. In some instances the first area to consolidate was the first to show resolution; in other cases clearing began concurrently with, or even followed, the later areas of involvement. Two cases showed resolution and spread occurring simultaneously in different areas.

Visceral displacement as seen in the roentgenogram was generally manifested as an elevation of the diaphragm on the affected side. This occurred in at least eighteen of the twenty-seven cases in which the diaphragm was visualized. In seven cases of the total series a slight shift of the mediastinum toward the lesion was demonstrated, but in no instance was this displacement comparable to that seen in massive collapse of the lung. Mediastinal displacement was not seen in the fourteen cases observed within thirty hours or less after the onset of the disease.

MECHANISM OF PAIN IN GASTRIC AND DUODENAL ULCERS

VII. FURTHER OBSERVATIONS

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The voluminous literature on the mechanism of pain in ulcer has been reviewed and discussed in considerable detail in previous articles. It will suffice here to mention only the more noteworthy contributions. Talma [1] in 1884 reported the production of severe epigastric distress by the injection of 500 cc. of a solution of hydrochloric acid (1:750) into the stomachs of two patients, one with a gastric carcinoma and the other, judging from the history, with a benign peptic ulcer. The distress induced was relieved by magnesium oxide. Suyling [2] confirmed both of these observations in 1888, and he concluded that hyperesthesia for dilute hydrochloric acid is frequently the cause of gastric pain. Bönniger [3] reported in 1909 that the distress of gastric ulcer could be brought on regularly by the introduction into the empty stomach of from 100 to 200 cc. of a tenth-normal solution of hydrochloric acid. In 1912, Sippy [4] stated that "the pain and discomfort of uncomplicated ulcer are due to the irritative action of hydrochloric acid on the nerves exposed in the ulcer." In 1923, in discussing the essential factors in the production of ulcer pain, Sippy [5] again declared:

> Clinically a high degree of free hydrochloric acid is practically always present. . . . It is practically certain that free hydrochloric acid is the important element in the irritant. At least it is constantly associated with the irritant. Clinically, distress attributed to uncomplicated ulcer is found only when the fluids of the stomach contain free hydrochloric acid in adequate concentration.

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1. Talma: Zur Behandlung von Magenkrankheiten, Ztschr. f. klin. Med. **8**:407, 1884.

2. Suyling, J. P.: Beitrag zur Kenntnis der Hyperaesthesie für Salzsäure, Berl. klin. Wchnschr. **25**:869, 1888.

3. Bönniger, M.: Zur Diagnose des Ulcus ventriculi, Berl. klin. Wchnschr. **45**:396, 1908.

4. Sippy, B. W., quoted by Musser, J. H., and Kelly, T. C.: Handbook of Practical Treatment, Philadelphia, W. B. Saunders Company, 1912, vol. 2, p. 349.

5. Sippy, B. W., in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1923, vol. 3, p. 132.

These statements were made on the basis of innumerable aspirations of the stomach during the presence of ulcer distress, although no figures or statistics are recorded. On the other hand, Löwenthal,[6] Schmidt,[7] Boring,[8] Hurst[9] and Reynolds and McClure[10] had introduced varying amounts of hydrochloric acid into the empty stomach in concentrations of from 0.5 to 2 per cent without producing distress either in normal persons or in patients with ulcer.

In 1926, one of us (W. L. P.[11]), working on patients with ulcer during periods of rather marked spontaneous distress and therefore with sensitive pain-producing mechanisms, drew the following conclusions with regard to ulcer distress:

1. It may be relieved by emptying the stomach.
2. It may be made to reappear by reinjecting the aspirated gastric content.
3. It is not initiated by introducing into the stomach aspirated gastric content in which the free acidity has been neutralized by alkali.
4. It may be made to reappear by injecting pure solutions of hydrochloric acid of normal and entirely physiologic concentration (0.2 to 0.3 per cent) or by stronger solutions (0.5 per cent).
5. It may be initiated by other chemical irritants such as dilute solutions of sulphuric acid, acetic acid and sodium hydroxide.
6. The distress so produced is relieved by the removal or neutralization of the chemical irritant.
7. The distress is the patient's typical pain both in type and in location, varying in severity from a mild discomfort to excruciating pain. It may or may not be as severe as the patient's usual distress.
8. Such distress is not ordinarily produced by similar injections into the normal stomach or in patients with ulcer during spontaneous or induced remissions.
9. The pain may be initiated by the acid gastric secretion excited by the subcutaneous injection of histamine.

It was also noted that in some normal patients, as well as in patients with ulcer, the acid solutions occasionally produced a mild sensation of

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6. Löwenthal, Max: Beiträge zur Diagnostik und Therapie der Magenkrankheiten, Berl. klin. Wchnschr. **29**:1188, 1892.

7. Schmidt, J. E.: Ein Beitrag zur Frage der Magensensibilität, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **19**:278, 1909.

8. Boring, E. G.: The Sensations of the Alimentary Canal, Am. J. Psychol. **26**:48 (Jan.) 1915.

9. Hurst, A. F.: Goulstonian Lectures on the Sensibility of the Alimentary Canal, New York, Oxford University Press, 1911.

10. Reynolds, L., and McClure, C. W.: Motor Phenomena Occurring in Normal Stomachs, in Presence of Peptic Ulcer and Its Pain, as Observed Fluoroscopically, Arch. Int. Med. **29**:1 (Jan.) 1922.

11. (*a*) Palmer, W. L.: The Mechanism of Pain in Gastric and Duodenal Ulcers: II. The Production of Pain by Means of Chemical Irritants, Arch. Int. Med. **38**:694 (Dec.) 1926 (in this article, page 703, line 4 should read, "55 cc. of gastric juice injected"); (*b*) ibid., p. 700, exper. 393.

epigastric warmth and burning, at times associated with nausea and even severe emesis. These symptoms were recognized by the patients with ulcer as entirely independent of the ulcer syndrome, and were probably due to duodenal irritation.[12]

As a result of these observations, it was concluded that hydrochloric acid is the irritant normally present in the gastric content which constitutes an adequate stimulus to the pain-producing mechanism of a sensitive peptic ulcer. Kymographic and roentgenologic studies[13] were undertaken at that time in an effort to determine the manner in which the acid produced the distress. It was found that in the great majority of the patients there was no relationship between ulcer pain and gastric peristalsis, duodenal peristalsis, gastric tone, the condition of the pylorus or that of the duodenal bulb, but that in occasional instances of intermittent, and also of remittent, pain the waves of pain, or the exacerbations in it, corresponded exactly with the peristaltic contractions of the stomach as recorded by the kymograph. These observations confirmed the previous findings of Ginsburg, Tumpowsky and Hamburger,[14] Carlson[15] and Hardt.[16] It was noted that the cases in which gastric peristalsis constituted an adequate stimulus to the pain-producing mechanism were ones with unusually severe pain, and, furthermore, that after the sensitivity of the pain-producing mechanism subsided, gastric peristalsis

12. Palmer, W. L.: The "Acid Test" in Gastric and Duodenal Ulcer; Clinical Value of Experimental Production of Typical Distress, J. A. M. A. **88**:1778 (June 4) 1927.

13. Palmer, W. L.: (*a*) The Mechanism of Pain in Gastric and Duodenal Ulcers: III. The Rôle of Peristalsis and Spasm, Arch. Int. Med. **39**:109 (Jan.) 1927. (Some errors occurred in this article which I should like to correct here. Mention of figures 2 and 8 was omitted from the text, and the numbers of all illustrations as given in the text, except figure 1, are therefore incorrectly given. Reference to figure 2 should be inserted in the last line on page 112 following "The fourth tracing"; hence "figure 2" in the seventh line on page 113 should read "figure 3"; "figure 3" in the fourteenth line on the same page should be "figure 4," and so on down to page 117, in the fourteenth line of which "figure 8" should be inserted after the word "tracing." From here on the references to the illustrations should be increased by two; i. e., "figure 4" in the twenty-first line on page 117 should be "figure 6"; "figure 7" in the thirty-seventh line on page 120 should be "figure 9," etc. On page 128, columns 2 and 3 of table 4 should be headed "Acid Test.") (*b*) Ibid., p. 124; (*c*) p. 131; (*d*) p. 116, fig. 7; (*e*) p. 129.

14. Ginsburg, Harry; Tumpowsky, Isidor, and Hamburger, W. W.: Contributions to the Physiology of the Stomach: XXXV. The Newer Interpretation of Gastric Pain in Chronic Ulcer, J. A. M. A. **67**:990 (Sept. 30) 1916.

15. Carlson, A. J.: Contributions to the Physiology of the Stomach: Origin of Epigastric Pains in Cases of Gastric and Duodenal Ulcer, Am. J. Physiol. **45**:81 (Dec.) 1917.

16. Hardt, L. L. J.: Pain in Active Pathologic Processes in Stomach or Duodenum, J. A. M. A. **70**:837 (March 23) 1918.

became painless at a time when pain could still be induced by the introduction of acid solutions into the stomach. It was also found that pain could be induced by the injection of acid into the stomach, in spite of preliminary atropinization and that it was not relieved by the intravenous injection of dextrose. The conclusion was reached that under certain conditions gastric peristalsis, as well as hydrochloric acid, constitutes an adequate stimulus to the pain-producing mechanism. Acid sensitization, however, seemed to be an essential prerequisite for the mechanical production of pain. The exact mechanism by which pain was produced by the acid and by gastric peristalsis was not clear. There was reason to think that it arose from the lesion itself, that peristalsis evoked pain as the result of mechanical irritation of the highly sensitive inflamed area, and that the acid likewise acted in some way directly on the ulcer. It was suggested that the mechanism might consist of the production of edema in the tissue about the edge of the ulcer, of localized muscular spasm or of direct irritation of exposed nerve endings.

Since the publication of this work, other investigators have described findings in part confirming and in part disagreeing with it. It seems advisable to analyze these reports in more or less detail. Cobet and Gutzeit,[17] in 1926, found that the injection of small amounts of dilute hydrochloric acid into the stomach produced distress in only two cases. On the other hand, they were unable roentgenologically to correlate ulcer pain with spastic and peristaltic changes in the stomach. Consequently they concluded that their attempts to produce spasm or pain by means of either electrical or chemical (acid) irritation in gastric ulcer had been unsuccessful. Berg,[18] in 1926, was also unable to make out any clear relationship roentgenologically between pain and gastroduodenal spasm or motility.

Hess and Faltitschek,[19] in 1928, in an important communication described almost total gastric spasm without pain in cases of tumor of the brain, Parkinson's disease and multiple sclerosis. The spasm was thought to be of central origin, due to irritation of the vagus. These authors also ascribed the regional gastric spasm described by Assmann [20] and others in tabetic crisis to central stimulation of the vagus. The absence of pain in the conditions mentioned was attributed by Hess and Faltitschek to central inhibition of the pain sense, but evidence in sup-

17. Cobet and Gutzeit: Zur Entstehung der Spasmen und Schmerzen beim Magengeschwür, Deutsches Arch. f. klin. Med. **150**:295, 1926.

18. Berg, H. H.: Die direkten Röntgensymptome des Ulcus duodeni und ihre klinische Bedeutung, Ergebn. d. med. Strahlenforsch. **2**:320, 1926.

19. Hess and Faltitschek: Ueber Gastrospasmus bei organischen Nervenleiden, Wien. klin. Wchnschr. **41**:1366, 1928.

20. Assmann, Herbert: Klinische Roentgendiagnostik der inneren Erkankungen, ed. 3, Leipzig, F. C. W. Vogel, 1924, p. 463.

port of this hypothesis is not presented. Painlessness, lack of muscular rigidity and lack of local hyperesthesia are considered by them to be characteristic of gastric spasm of central origin. No evidence is offered, however, to prove that gastric spasm of peripheral origin is painful.

In the same year, Poulton [21] advanced the theory that visceral pain is due not to peristalsis, or to peristalsis and ballooning as suggested by Hurst,[22] but to stretching with consequent deformity of the nerve endings subserving the sense of pain, situated in the walls of the viscus: ". . . I would support the view that visceral pain is an affair of the whole visceral wall and not of any isolated lesion in it, and that peptic ulcer produces painful effects secondarily by causing reflex increase of tone." The experiments cited in support of this were performed on the esophagus. The evidence offered in the two cases of ulcer described is entirely inadequate, although in one record (fig. 8) some relationship is to be noted between the variations in pain and the variations in intragastric pressure. Poulton disposes of the hypothesis that pain results from the mere contact of the ulcer with acid by the statement that the suggestion is now so generally discredited that he need only mention the fact that pain may be present with peptic ulcer when there is no free acid in the stomach. Proof of this is not offered. The production of pain in some cases by the introduction of acid into the stomach, according to Poulton, is presumably due to an increase in tonus. It was shown by Palmer,[13] and it may be seen again in the tracings presented in the present paper, that ulcer pain is not dependent on or accompanied by changes in intragastric pressure or gastric tone.

Wilson [23] in 1928, on the basis of roentgenologic observations, concluded that in duodenal ulcer, pain bears no relationship to gastric peristalsis or to the chemical reaction of the gastric content, but is due to a sustained contraction of the duodenal bulb. The act of squeezing the gastric content into the contracted bulb and thereby dilating it relieved the pain in thirteen of sixteen cases. The three protocols cited are not convincing. The maneuver employed is one commonly used in roentgenology and gives only momentary filling of the bulb. Apparently the relief observed by Wilson was also momentary. Another factor to be considered in appraising this work is that the external manual pressure of the palpating hand produces in effect a counter-irritant and possibly relieves the pain momentarily in this manner. Wilson's work is also not

21. Poulton, E. P.: Oliver-Sharpey Lectures on an Experimental Study of Certain Visceral Sensations, Lancet **2**:1223 and 1277, 1928.

22. Hurst, A. F.: Brit. M. J. **1**:145, 1925.

23. Wilson, M. J.: Duodenal Ulcer: Observations on the Behavior of Stomach and Duodenum in the Presence of Pain, Arch. Int. Med. **41**:633 (May) 1928.

in accord with the previous findings of other observers.[24] It is interesting in this connection to note that MacLeod [25] has attributed duodenal ulcer pain to distention of the duodenal cap with gas, offering as evidence experiments in which pain was caused by injecting air into that portion of the intestine. The production of pain mechanically in this way, however, is quite compatible with observations to be described in this report. Palmer [13b] showed originally, however, that distention of the bowel at a point distal to the ulcer might produce pain indistinguishable to the patient from typical ulcer distress.

Hardy [26] studied the problem of pain in 1929, using a modified "acid test" [12] and took exception to the conclusion that acid is the normal stimulus for the pain-producing mechanism. His reasons were, in part, the following:

> The pain is rarely severe and the patient, though able to identify it, will often volunteer the information that it is not nearly as severe as his typical distress, and this, be it noted, in the presence of acid values far in excess of those ever present in health or disease. The pain rarely shows itself when the acid concentration is at its maximum, that is, immediately after its introduction.

It is true that the pain is frequently not as severe as the spontaneous distress, but, on the other hand, it is not at all uncommon in our experience for the patient to writhe in agony and to give every manifestation of a person in severe pain. Hardy's results may be due in part to his modification of the test; he emptied the stomach at the end of each thirty minutes before the further injections of the acid. Still more important, in our opinion, is Hardy's failure to give adequate consideration to the factor of *time*. Pain seems to be the product of at least three factors: the sensitivity of the lesion, the concentration of the acid and the length of time the acid is in contact with the lesion. If the sensitivity is great, the concentration of acid required is lower and the interval of time shorter. Conversely with less sensitive ulcers, the requisite concentration of acid and interval of time are greater. Indeed the interval of time may exceed the duration of the experiment, as is clearly the case when no pain appears during the test, but develops a few minutes later when the patient has returned to his ward.[27]

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24. Homans, John: The Relation of Pain in Gastric and Duodenal Ulcer to Muscular Activity of the Stomach, Am. J. M. Sc. **157**:74 (Jan.) 1919. Reynolds and McClure.[10] Palmer.[18] Berg.[18]

25. MacLeod, Donald: Pain in Relation to Duodenal Ulcer, Lancet **2**:1358, 1929.

26. Hardy, T. L.: The Role of Hydrochloric Acid in the Causation of Gastric Pain, Lancet **1**:711 (April 6) 1929.

27. Palmer, W. L.: Certain Phases of the Ulcer Problem, M. Clin. North America **13**:413, 1929, cases I and II.

The same factors are operative when attempts are made to evoke pain by means of secretion induced by injection of histamine hydrochloride. Hardy's experiments gave negative results. We feel that the product of ulcer sensitivity and time were inadequate, for under proper conditions, ulcer pain may be initiated by histamine secretion as was evident in the earlier observations [11b] and as we shall show again in the present report.

Hurst,[28a] in 1929, discussed the subject of ulcer pain in considerable detail and concluded that while hydrochloric acid does constitute an adequate stimulus for the pain-producing mechanism, the effect is not due to mere contact of the ulcer with the acid. He was brought to this view by the known fact that the stomach and intestines are insensitive to tactile, thermal and chemical stimuli, and because he had satisfied himself, through the use of the stomach tube in the case of ulcers of the stomach and of the sigmoidoscope in those of the colon, that ulcers are as insensitive to these stimuli as is the healthy mucous membrane. The latent period noted in Palmer's earlier experiments was considered by him as additional evidence that the contact of the ulcer with the acid is not the cause of the pain. Hurst concluded that the "pain of duodenal ulcer depends upon an increase of tension which develops in some way when a small quantity of acid contents is present in the stomach." He elaborated on this view and developed the theory that this increase in tension occurs in the pyloric vestibule, and is due to achalasia and spasm of the pyloric sphincter plus deep peristaltic waves which by the time they reach the vestibule almost completely separate its contents from those of the proximal portion of the stomach. Consequently the pressure in the small distal segment rises unless the pyloric sphincter at the same time relaxes; if, for any reason, the sphincter does not relax, the pressure rises greatly.

The rise in pressure in the pyloric vestibule produces an abnormal degree of tension in the individual fibers of the muscular coat of this segment of the stomach. This is the actual cause of the pain, the rise in tension being the adequate stimulus required to produce the afferent nervous impulses which give rise to the sensation of pain.

The pain of gastric ulcer may occur independent of the condition of the pyloric sphincter, but Hurst ascribes this to an increase in pressure in the proximal portion of the stomach, the obstruction at the site of the ulcer being due apparently to a spasmodic hour glass constriction which "is frequently rendered more complete by the simultaneous pres-

28. (*a*) Hurst, A. F., and Stewart, M. J.: Gastric and Duodenal Ulcer, New York, Oxford University Press, 1929, pp. 26 and 154; (*b*) ibid., p. 158; (*c*) ibid., p. 44; (*d*) ibid., p. 453.

ence of orthostatic hour glass constriction or organic hour glass constriction or by the presence of both."

The argument is based, in part, on the previously mentioned conclusion of Wilson [23] that ulcer pain disappears when the pylorus relaxes and the bulb fills out. Palmer's original roentgenologic observations on the complete absence of any relationship between pain and gastric peristalsis, spasm of the pylorus or spasm of the duodenal bulb, Hurst disregarded because they were made under artificial conditions, that is, with an acid solution of barium sulphate. He also pointed out that in three pairs of the roentgenograms shown, the lumen of the pyloric canal was half or less than half the width in those taken when pain was present compared with those taken after its disappearance, but he ignored the fact that direct fluoroscopic observation had shown this to be of no significance, owing to the constantly varying configuration of the stomach. Furthermore, it was obvious in these original roentgenograms, it seems to us, particularly in the first and last pair, that not only was the pylorus patent and the duodenal bulb well filled during the presence of pain, but also that a peristaltic wave of sufficient intensity to block off the contents of the pyloric vestibule from those of the main part of the stomach was not present. It is apparent, therefore, that the intragastric pressure in the vestibule must have been the same as that in the remainder of the stomach. Furthermore, it was clearly shown kymographically at that time that ulcer pain is entirely independent of changes in the intragastric pressure and therefore independent of changes in tension or tone in the body of the stomach or in the vestibule. In the work to be reported here we shall present further roentgenologic and kymographic confirmation of these findings.

In 1930, however, Smith, Paul and Fowler,[29] studying ulcer pain by the kymographic method, arrived at the conclusion that pain depends not on the reaction of the gastric content but on an increase in tone and peristaltic action. "In each case studied during distress, the pain corresponded with an increase in tone and the passage of a peristaltic wave." The intravenous injection of 1/50 grain (0.0013 Gm.) of atropine sulphate promptly relieved the distress. This work is described in greater detail in a subsequent article by Smith and Paul [30] in which they state that their "findings are in accord with the observations of Ginsburg, Tumpowsky and Hamburger, Carlson and Hardt . . . These observations support the contention of Hurst and Ryle, that the pain is primarily dependent on an increase in the intragastric tension." The

29. Smith, F. M.; Paul, W. D., and Fowler, W. M.: Alterations in the Gastric Function Associated with Gastric and Duodenal Ulcer, Tr. A. Am. Physicians **45**:377, 1930.

30. Smith, F. M., and Paul, W. D.: Studies on the Mechanism of the Pain of Peptic Ulcer, Ann. Int. Med. **5**:14, 1931.

method employed by Smith and Paul consisted of anchoring a water-filled balloon in the pyloric section of the stomach. The tracings shown do not entirely support the statement that "The pain corresponded with an increase in tone and the passage of a peristaltic wave." The method used by them does not record intragastric tension, but rather the pressure exerted by the antral musculature on an anchored bag. Their observations do, however, further confirm those of other workers, including Palmer, bearing on the adequacy of mechanical stimuli in the production of pain in sensitive ulcers.

Gutzeit,[31a] in 1929, after considering the more or less contradictory evidence on the subject of gastric pain, concluded that its origin was not yet known. He considered that muscular contraction itself could be painful because von Bergmann had observed severe pain from the powerful contraction of the pyloric muscle around a piece of cabbage. Gutzeit himself during a gastroscopic examination had seen pain appear suddenly when the relaxed sphincter contracted and narrowed the gastric lumen, confirming an observation of Schindler's. This pain was exactly the same as the patient's spontaneous pain. It continued after the air distending the stomach had been allowed to escape through an opening in the gastroscope; hence it was not a pain from distention but one from muscular contraction. There is no reason to question these observations. It has been recognized for years that gastric motor activity may produce pain. The epigastric pangs of hunger have been shown by Cannon and Washburn,[32] Carlson [33] and numerous other investigators to be due to contractions of the empty stomach. On the other hand, such peristalsis is commonly not accompanied by pain [34] and, as has been mentioned previously, painless spasm of the stomach has been observed. Furthermore, ulcer pain occurs during the digestive cycle, and digestive peristalsis is painless. The conditions under which gastric motor phenomena result in pain are not yet clear.

Gutzeit also pointed out that ulcer-like pains are not characteristic of ulcer alone but may be seen with pure gastritis without gross ulceration. These observations are in accord with the findings of Konjetzny,[35] but do not affect the problem of ulcer pain particularly. Gastritis is an

31. (*a*) Gutzeit, Kurt: Die Gastroskopie im Rahmen der klinischen Magendiagnostik, Berlin, Julius Springer, 1929, p. 26; (*b*) ibid., p. 77.

32. Cannon, W. B., and Washburn, A. L.: An Explanation of Hunger, Am. J. Physiol. **29**:441, 1912.

33. Carlson, A. J.: The Control of Hunger in Health and Disease, Chicago, University of Chicago Press, 1916.

34. Heinz, T. E., and Palmer, W. L.: A Study of the Effect of Insulin on Gastric Motility, Proc. Soc. Exper. Biol. & Med. **27**:1047, 1930.

35. Konjetzny, G. E.: Entzündliche Genese des Magen-Duodenalgeschwürs, Arch. f. Verdauungskr. **36**:214, 1925.

ulcerative process. The lesions are small and superficial, but nevertheless ulcerative and surrounded by an inflammatory reaction. Furthermore, Gutzeit observed, and we likewise have repeatedly noted, that there is no correlation between the size of the lesion and the severity of the pain. Gutzeit ascribes this variability to individual differences in response to pain, but does not know whether this is due to variations in conduction or perception of pain or to other factors.

Christensen,[36] working in Knud Faber's clinic in Copenhagen, made a careful study of so-called "hunger pain" in 1931. By "hunger pains" she meant the "cardialgia appearing at times when the stomach is presumably empty or nearly empty, and of which the patient gives the information either that it is relieved by the intake of food or, at any rate, that he has never tried if it is so." She gathered her material without attaching any particular importance to the verification of the diagnosis of ulcer and insisted merely on the presumably unquestionable presence of the so-called "hunger pain." However, in the protocols it is apparent that the diagnosis of ulcer was made in the majority of the cases. It seems fair to assume that most of the pain which she studied was ulcer pain. She concluded:

> . . . the pains have never been present without the gastrographic curve showing a concurrent contraction period. There was never any registration of an attack of pain during a period of absolute rest. The pain registration would always begin sooner or later after a contraction period had started and they would cease when this period was replaced by absolute rest or a few minutes after.[36b]

The pain registered by the patients was of two types: first, a continuous pain throughout the period of contraction, and second, intermittent pain. Examination of the gastric content was interpreted to show that

> . . . there was no relation whatever between the spontaneous variations in the acidity of the stomach content and the appearance or the intensity of the pain. Nor was the pain affected by the artificial production of very low acidity values (acid deficit of several hundreds).[36c]

Relief of pain following the ingestion of sodium bicarbonate without any influence on the gastric contractions was noted by her as it had been noted by Ortmayer.[37] Christensen thought it

> . . . reasonable to assume that the relief has nothing to do with the alkaline reaction and that it is due to the carbon dioxide which is liberated on the mixture of hydrochloric acid and sodium bicarbonate. For, as is well known, carbon dioxide has a strong anesthetizing effect on the mucous membrane. . . . These examinations then show no relation whatever between the variations in the acidity of

36. (*a*) Christensen, Olive: Pathophysiology of Hunger Pains, Copenhagen, 1931, p. 78; (*b*) ibid., p. 79; (*c*) ibid., p. 102; (*d*) ibid., p. 103.

37. Ortmayer, Marie: Gastric Motor Activity in Patients with Peptic Ulcer, Arch. Int. Med. **35**:423 (April) 1925.

the stomach content and the variations in the spontaneous pain that may be observed during a single examination of a few hours' duration. This, however, does not exclude the possibility that the pain may be appearing only on days or in periods when the acidity on the whole is rather high.[36d]

Her criticism of Palmer's earlier work is based apparently on two points: first, that the pain usually studied was an "artifact pain" produced by repeatedly filling the inflamed stomach with large amounts of an acid sufficiently concentrated to produce an uncomfortable burning when injected into a normal stomach, and second, that she could see no correlation between the acidity of the gastric content at a given time and pain at the same or nearly the same time. In answer to the first criticism, that the pain produced was "artifact pain," it is necessary only to point out that Christensen seems to have overlooked the fact that pain was produced repeatedly by the introduction of *normal gastric content* and of perfectly *physiologic concentrations of hydrochloric acid* (from 0.2 to 0.3 per cent). The second criticism, the lack of correlation between the intensity of the pain and the degree of acidity present, is also not valid, for it ignores the factor of *time*, the significance of which has become increasingly apparent to us throughout our work. In some very sensitive ulcers severe pain may be produced immediately by the introduction of acid into the stomach; in others, a very variable interval elapses before distress appears. The pain may begin as a mild discomfort, gradually and continuously increasing in severity until it becomes an excruciating cramp. This gradual increase in the severity of the pain, it seems to us, must also be the result of time. As was mentioned previously in discussing Hardy's work, one must consider pain as the product of ulcer sensitivity, acid concentration and time.

In 1927 one of us (W. L. P.) examined some of Christensen's tracings. They are excellently reproduced in her monograph. There can be no question as to the facts presented by her, but there is a definite difference in opinion as to the interpretation of these facts. The intermittent pain described by Christensen in ulcer is similar in all respects to the intermittent pain described by Carlson [15] and by us. This distress is definitely correlated with gastric activity. The continuous spontaneous pain seen by Christensen is correlated with gastric activity only to the extent that it appears at some time after the beginning of a period of contraction and continues until after the end of this phase. It was not found to appear during a period of rest. Christensen worked with patients whose stomachs contained only a small amount of content. The experimental subject was allowed to lie on his back, propped up slightly by pillows. Under these conditions it is certain that the stomach does not empty its content continuously into the duodenum, for it may be shown roentgenologically that in the supine position, small amounts

of barium sulphate will remain in the most dependent portion of the stomach, the fundic region, during periods of gastric quiescence until, with the onset of peristalsis, the barium sulphate is gradually carried up over the spine into the pyloric segment and the duodenum, bathing the surface of the ulcer with chyme. With a sufficiently sensitive mechanism, an adequate concentration of hydrochloric acid and time, pain results. It is noteworthy that free hydrochloric acid was present in Christensen's experiments at the time of pain. The continuous pain observed by her in periods of gastric activity is thus explained. Careful examination of the numerous protocols has failed to reveal to us any evidence opposed to this concept.

A significant study of the effect of nitrites on pain and on the motility of the gastro-intestinal tract has recently been reported by Beams.[38] He confirmed the earlier work of Holmes and Dresser [39] and found that in 95 per cent of the cases studied, nitrites inhibited gastric peristalsis and diminished gastric tone. The effect lasted from two to five minutes with amyl nitrite, and from five to ten minutes with spirits of glyceryl trinitrate.

> Amyl nitrite gave complete relief from pain in twelve of the twenty patients with duodenal ulcer, partial relief in four, and no relief in four. The pain was relieved for from five to twenty minutes. . . . Six (of the ten) patients with gastric ulcer obtained relief of pain for from five to fifteen minutes after inhalation of amyl nitrite, whereas in four patients with penetrating gastric ulcer the pain was not controlled. In three patients with pyloric stenosis proved by operation in whom visible peristalsis was observed, amyl nitrite not only relieved the pain but caused cessation of the peristalsis. The peristalsis disappeared more promptly than the pain, but reappeared in from three to five minutes while the pain was relieved for from five to ten minutes.

Apparently in those cases in which temporary relief of pain occurred, it was due to the effect of the medication on the musculature, although the other effects of the medication, such as throbbing in the head, slight dizziness or a warm flushed feeling, may have played more of a rôle than has been recognized. Beams feels that this evidence supports the theory that ulcer pain is dependent on the motility and tone of the stomach rather than directly on the acidity, although he considers the acidity to be an important factor in the pain. It is to be noted, however, that he did not observe ulcer pain in the continued absence of free acidity. The further significance of his observations will be discussed later.

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38. Beams, A. J.: The Effect of Nitrites on the Motility of the Gastro-Intestinal Tract: Clinical Study, Arch. Int. Med. **49**:270 (Feb.) 1932.

39. Holmes, G. W., and Dresser, Richard: The Use of Amyl Nitrite as an Anti-Spasmodic, Am. J. Roentgenol. **19**:43 (Jan.) 1928.

Vanzant and Snell [40] have recently reported a study of the effect of the injection of nonspecific protein on the pain of ulcer and on gastric secretion with the following conclusions:

> In cases of ulcer, the injection of foreign protein was frequently followed by a gratifying reduction in the amount of pain and distress. This clinical improvement was not associated with any consistent lowering of the gastric acidity and there was no correlation between the degree of acidity found at any one time and the amount of pain complained of. . . . There was some evidence to indicate that more lasting relief of symptoms can be expected in those cases in which the secretion is reduced after treatment. . . . We have no exact information which would warrant our making guesses as to the mechanism which in some cases produces prompt relief of pain and discomfort.

It has been recognized for many years that during the pain-free periods of ulcer the gastric acidity is practically the same as during the periods of pain. This has little bearing on the rôle of acidity in the production of pain, for in the one instance the acid acts on a sensitive, and in the other instance on an insensitive, mechanism. Of the three variables, sensitivity of the ulcer, time and concentration of the acid, Vanzant and Snell studied chiefly the acid factor. They apparently found it to be invariably present, but were unable to correlate the degree of acidity with the severity of the pain at a given time. This was probably due to the fact that the difficult variables of time and of sensitivity of the ulcer entered in.

Meyer, Fetter and Strauss [41] concluded from their investigations on the relation of ulcer pain to gastric motility and acidity that "the patients were found to fall into two classes: (1) those who had pain response to an acid stimulus but showed no pain in relation to gastric motility and (2) those who had no pain response to an acid stimulus but had pain during periods of gastric motility." In their case 1, illustrative of eight showing pain in response to an acid stimulus, distress developed with the perfectly physiologic concentrations of acid found in the patient's own gastric juice—a significant observation confirming our own work—and appeared also following the introduction of acid into the stomach; relief was obtained on withdrawal of the acid and the administration of sodium bicarbonate. Gastric motility, as recorded kymographically, was independent of pain. In case 2, illustrative of six cases showing pain during periods of gastric motility, pain did not develop from the injection of acid, although this was tried on two occasions. Three days later a relationship of the pain to gastric motility was demon-

40. Vanzant, F. R., and Snell, A. M.: The Effect of Injection of Nonspecific Protein on the Pain of Ulcer and on Gastric Secretion: A Clinical and Experimental Study, J. Clin. Investigation **11**:647 (July) 1932.

41. Meyer, Jacob; Fetter, Dorothy, and Strauss, A. A.: The Relation of Pain in Peptic Ulcer to Gastric Motility and Acidity, Arch. Int. Med. **50**:338 (Aug.) 1932.

strated. The failure of the "acid test" to evoke pain in this instance is somewhat puzzling, but the phenomenon is one observed by us also, and discussed elsewhere.[42] However, we feel that Meyer, Fetter and Strauss are not justified in excluding the acid factor. The patient's stomach was known to secrete free hydrochloric acid, a free acidity of 25 having been found on one occasion and one of 35 on another. No determination of the degree of gastric acidity was made during the motility test in this experiment. In view of the aforementioned observations [13] with regard to acid sensitization as a prerequiste in the pain of ulcer it seems necessary to insist that to consider motility as the sole cause of the pain it must be shown to be effective in the *continued absence of free hydrochloric acid*. This evidence has not been adduced as yet.

Various observers have attempted to induce ulcer distress by the direct application of acid to the surface of the ulcer by means of a duodenal tube or at operation. Reynolds and McClure,[10] using a Rehfuss tube, the tip of which was ascertained by fluoroscopy to be in the duodenal bulb at the site of the lesion, were unable to produce pain or any other subjective sensation even though pylorospasm, cessation of gastric peristalsis and duodenal antiperistalsis were induced. Schüle,[43] on the other hand, using the same technic, was successful and suggested it as a method for determining the presence of a duodenal ulcer. Meyer, Fetter and Strauss [41] introduced 50 cc. of a 0.5 per cent solution of hydrochloric acid directly into the duodenum and apparently produced pain in some cases (number not stated). These same observers failed to produce distress in four cases of gastric or duodenal ulcer in which hydrochloric acid in dilutions of 0.5 per cent, 1 per cent and 5 per cent was applied directly to the ulcer during operation under local anesthesia. Two of these patients previously had given definitely positive responses to the "acid test" and two to the "motility test." Failures such as these in the production of pain by the application of acid at operation are not surprising, for while the factors of ulcer sensitivity and of acidity may be adequate under ordinary conditions for the production of pain, the time factor is almost necessarily inadequate. The surgeon who applies the acid to the surface of the ulcer is naturally unwilling to wait more than a few minutes to observe its effect. Hence in order for such an experiment to be positive it is necessary for the ulcer to be at the moment in such a high state of irritability that the application of acid will evoke pain instantly or within a few moments. This is rarely the case, as is shown by the interval of from several minutes to an hour or more which usually elapses even under normal conditions between the development of a good acidity (be it from the

42. Palmer (footnotes 11 and 12).

43. Schüle, A.: Zur klinischen Diagnostik des Ulcus duodeni, München. med. Wchnschr. **73**:1191, 1926.

introduction of acid, the secretion induced by injection of histamine hydrochloride, or the secretory response to ingestion of food) and the appearance of pain. Consequently we are not inclined to attach much significance to these seemingly crucial but negative experiments.

Meyer, Fetter and Strauss did not mention whether or not pain was produced by mechanical stimulation of the ulcer area, as by pinching, although they stated that traction on the mesentery was painful.

Westphal and Katsch,[44] in operating on a patient with duodenal ulcer under local anesthesia, observed a powerful contraction of the pylorus associated with severe typical hunger pain as the result of electrical stimulation of the gastric antrum. They considered the normal mechanism of pain to be that of pylorospasm induced by an exaggerated acid reflex. Lennander,[45] in operating on a perforated gastric ulcer under local anesthesia, noted that the inflamed walls of the stomach and intestine were quite insensitive to mechanical stimuli. This observation was confirmed by Morley [46] in two cases. Kinsella,[47] on the other hand, found experimentally that the normally insensitive bowel could be rendered sensitive to mechanical stimuli by the rapid injection of saline solution into the wall of the bowel. Ivy [48] had a similar experience.

Dragstedt and Palmer [49] reported one positive experiment in the mechanical and chemical production of ulcer pain during an operation on a patient under local anesthesia. The duodenal ulcer in this case was highly irritable as was shown by the excruciating spontaneous pain and the very severe pain produced by the acid test on the morning of operation. Dr. Dragstedt's description of his observation is as follows:

> A puckered scar was visible on the anterior wall of the duodenum about one centimeter distal to the pylorus. On very gently rubbing the serosa of this scar with the gloved finger the patient complained of pain similar to his ulcer distress. This pain persisted after the rubbing was discontinued. The patient was then told that something would be done to relieve his distress entirely, whereupon the region of the ulcer was rather firmly compressed between the thumb and forefinger of

44. Westphal, Karl, and Katsch, Gerhardt: Das neurotische Ulcus duodeni, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:402, 1913.

45. Lennander, K. G.: Beobachtungen über die Sensibilität in der Bauchhöhle, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **10**:94, 1902.

46. Morley, John: Abdominal Pain, New York, William Wood & Company, 1931, p. 71.

47. Kinsella, V. J.: The Mechanism of Pain Production in Abdominal Visceral Disease with Special Reference to the Pains of Peptic Ulcer, M. J. Australia **1**:64 (Jan. 21) 1928; Some Problems of the Normal and Pathological Physiology of the Stomach, Lancet **1**:1130, 1929.

48. Ivy, cited by Alvarez, W. C.: The Mechanics of the Digestive Tract, New York, Paul B. Hoeber, Inc., 1928, p. 145.

49. Dragstedt, L. R., and Palmer, W. L.: Direct Observations on the Mechanism of Pain in Duodenal Ulcer, Proc. Soc. Exper. Biol. & Med. **29**:753, 1932.

the operator and massaged gently but firmly. This produced severe distress. Several guide threads of fine silk were now introduced into the anterior wall of the pyloric antrum and by means of these traction was made on the duodenum pulling it toward the left. Every time this traction was made the patient complained of severe pain resembling his ulcer distress. While this distress was present and while the traction was continued twenty cubic centimeters of five per cent sodium bicarbonate solution were injected by means of a hypodermic needle into the lumen of the pylorus. The distress was almost immediately relieved, and this relief persisted for about five minutes. Twenty cubic centimeters of 0.5 per cent hydrochloric acid were then injected into the first portion of the duodenum in the same way, and almost immediately the patient complained of a burning type of pain. This persisted until an injection of sodium bicarbonate solution was made. The relief obtained from this last injection was not as striking as at first, and it did not persist. After about three minutes the patient complained of severe cramping pain which radiated up into his chest. This radiation had been frequently noted before in association with a cramping type of pain. Simultaneous with the appearance of this cramping pain there appeared a deep circular contraction ring just distal to the ulcer. This local spasm of the duodenum after a while passed distally only to be succeeded by several subsequent similar spasms. All during this time the patient complained of very severe cramp-like pain. It is interesting in view of this observation that several peristaltic waves were seen passing over the pyloric antrum at a time when no distress was experienced.

In our judgment these observations are highly significant. They show clearly that the ulcer pain in this case arose in the lesion itself, or in its immediate neighborhood, and not in the pylorus or in the gastric antrum. Furthermore, it was produced *mechanically* by rubbing or pinching the serosa above the lesion or as the result of a circular contraction ring appearing just distally to the lesion, and *chemically* by the injection of acid into the lumen of the duodenum where it presumably came into contact with the surface of the ulcer. Similarly the injection of alkali relieved the pain.

METHODS

The methods employed in the work to be herewith reported have been similar to those previously used and have included: clinical observation of the acidity of the gastric content during spontaneous distress, the production of ulcer pain by physiologic solutions of hydrochloric acid and by stimulation of gastric secretion with histamine hydrochloride, kymographic and roentgenologic studies of the stomach during distress, and observations on the effect of atropine sulphate and of calcium chloride on ulcer pain. We have not attempted to tabulate our data, feeling that the results are best presented by a careful consideration of certain illustrative protocols, kymographic tracings and roentgenograms. The group that was studied includes patients with benign gastric ulcer, duodenal ulcer and gastric carcinoma, in all of whom the clinical diagnosis was confirmed roentgenologically, except for one patient with recurrent ulceration following partial gastric resection in whom the diagnosis was based on clinical evidence only. Several of the patients were also operated on and the diagnosis was thus confirmed.

RESULTS

The following protocol was obtained during a study of the patient with recurrent ulceration following partial gastrectomy. The initial lesion in this case had been a duodenal ulcer for which a gastroenterostomy had been performed. A gastrojejunal ulcer had then developed, as was demonstrated at the second operation. A partial gastrectomy was performed. Following this the patient's typical ulcer distress recurred, accompanied at least on one occasion by tarry stools. This case is included because it is the only one of its kind which we have been able to study, and because the results are so typically those of ulcer distress.

CASE 1.—7:45 a. m.: The patient was awakened with pain which was relieved by a hot bath at 8.

8:15: Four ounces each of cream and milk were given.

9:50: The typical distress appeared below or around the navel on the left side.

10:20: The pain continued, with nearly the usual severity. Aspiration of the stomach (Rehfuss tube) yielded 17 cc. of green fluid, with a free acidity of 19. The distress became less.

10:25: The stomach was aspirated: 55 cc. of thick yellow green bile was obtained; the free acidity was 0. The distress was nearly gone.

10:30: The distress was entirely gone.

11:02 to 11:05: Two hundred cubic centimeters of a 0.4 per cent solution of hydrochloric acid was injected. Distress appeared during the injection, at 11:03.

11:10: The pain was quite severe, worse than at any time that day.

11:17: The patient felt very uncomfortable, as evidenced by writhing and moaning. Nausea appeared.

11:20 to 11:25: The stomach was aspirated, yielding 250 cc. of yellow liquid with a free acidity of 37. The distress at once became less severe and gradually diminished.

11:45: Aspiration of the stomach yielded 15 cc. of yellow liquid; the free acidity was 10.

11:50: The distress was practically gone; only a slight soreness remained.

11:55: The pain returned.

12:00 The stomach was emptied; 10 cc. of cloudy blood-tinged juice was obtained; the free acidity was 33.

12:10 p. m.: The pain continued; aspiration of the stomach yielded 6 cc. of fluid with a free acidity of 30.

12:20: The pain still continued, but was mild; aspiration of the stomach yielded, first, 12 cc. of clear fluid, and then 8 cc. of thick yellow fluid. The free acidity of the mixture was 18.

12:30: The distress was nearly gone. The stomach yielded 7 cc. of clear juice with a free acidity of 16.

12:40: The distress was practically gone. Aspiration yielded 20 cc. of cloudy thick yellow liquid with a free acidity of 0.

12:48 to 12:50: One hundred cubic centimeters of a fortieth-normal solution of sodium hydroxide was injected.

1:10: The patient was more free from distress during the last twenty minutes than he had been all forenoon. He felt entirely comfortable. The stomach was emptied, and 30 cc. of cloudy liquid was obtained; the free acidity was 6.

1:15: The patient became more uncomfortable.

1:25: The pain gradually grew more severe and was now as bad as ever. The stomach was aspirated, yielding 27 cc. of cloudy gray juice with a free acidity of 44. The patient groaned and writhed with pain.

1:35: The pain continued to be severe. The stomach was emptied; 20 cc. of cloudy gray liquid with a free acidity of 43 was obtained. There was slight easing of pain.

1:37 to 1:40: One hundred cubic centimeters of a tenth-normal solution of sodium hydroxide was injected.

2:07: The pain was nearly gone; the patient stated that he felt much better than previously.

2:10: The stomach was emptied, yielding 60 cc. of a yellow liquid with free acidity of 0. The pain was practically gone.

In this experiment spontaneous pain was present, with a free acidity of 19. Following aspiration, bile-colored duodenal content appeared in the stomach in sufficient quantity to neutralize the free acid completely. This was accompanied by complete relief of the distress for thirty minutes. Very severe distress was then produced immediately by the injection of 200 cc. of a solution of approximately 0.4 per cent hydrochloric acid. The stomach was aspirated from 11:20 to 11:25 a. m. with gradual but almost complete relief by 11:50. Ten minutes later the distress had returned. The free acidity was found to have risen to 33. The pain continued; the free acidity was still 30. Ten minutes later the free acidity had dropped; more duodenal content had appeared, and twenty minutes later, with a free acidity of 0, the pain was gone. Following the administration of 100 cc. of a fortieth-normal solution of sodium hydroxide the pain did not reappear for twenty-five minutes. It then gradually increased, and ten minutes later became very severe, at which time the free acidity was found to be 44. The pain continued, and the free acidity remained high until 1:40 p. m., when 100 cc. of a tenth-normal solution of sodium hydroxide was given, followed by relief in twenty minutes. Considering the constantly changing conditions produced by the irregular discharge of duodenal content into the stomach and the very important factor of *time*, it seems to us that this experiment demonstrates clearly the relationship between gastric acidity and ulcer pain.

Figure 1 shows the kymographic tracing made with the usual technic (a water manometer, a balloon located in the stomach and containing approximately 120 cc. of air, an air-filled system) in the case of a patient with an active, highly sensitive duodenal ulcer. Spontaneous pain was present at the beginning of the experiment (*A*, 11:55 a. m.), with a gastric acidity of 60, total 90. The stomach was emptied, 40 cc. being obtained, and the pain gradually subsided at *B* and *C* (12:03 and 12:06 p. m.), suddenly recurring four minutes later, at *D*. The sudden exacerba-

tion of the pain at *D* cannot be explained on the basis of a momentary increase in the gastric acidity. It is possible that the ulcer itself may suddenly have been the recipient of a few cubic centimeters of gastric

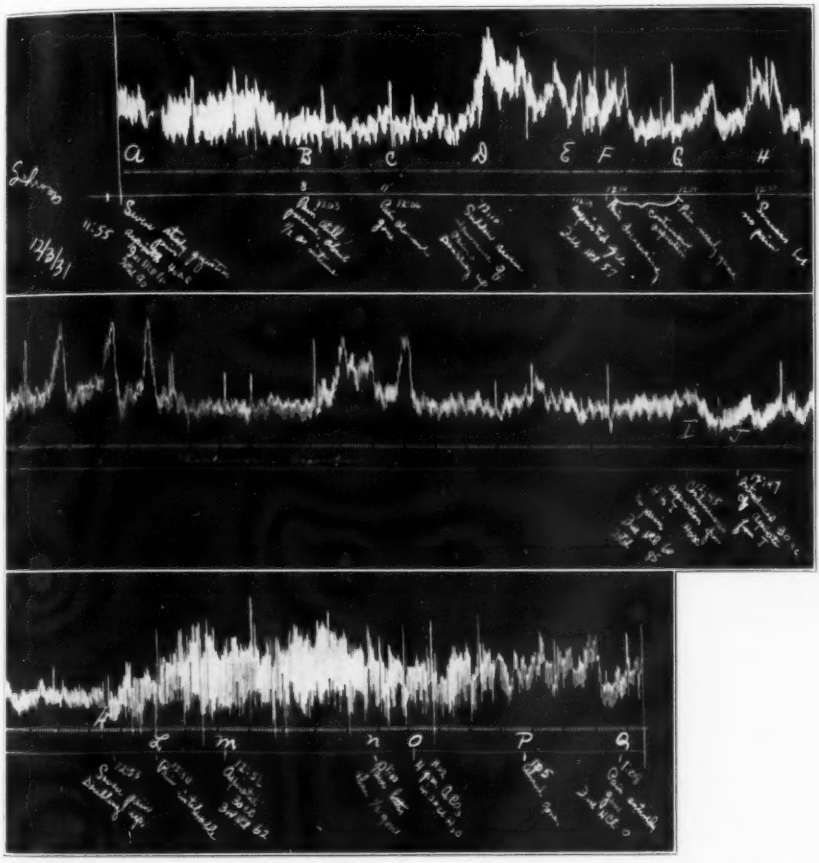

Fig. 1.—Kymographic tracing from a case of active duodenal ulcer showing: (1) the relief of pain following the emptying of the stomach; (2) the reappearance of severe pain subsequent to the reinjection of the normal acid gastric content, and (3) complete relief again after emptying the stomach and administering calcium carbonate. (The tracings are reduced to approximately one seventh of their natural size. The intragastric pressure is indicated by the height of the tracing above the base line.)

juice of a higher concentration than that previously present, but it is more probable that the sudden recurrence of the pain was due to spasm.

It is highly significant, however, that at *E* (12:13) the free acidity was still 57. The stomach was continuously aspirated, and at *H* (12:20) the pain was entirely gone, although some soreness persisted. Continuous aspiration of the stomach for twenty-five minutes from *H* to *I* (gastric content, 40 cc.; free acidity, 60; total, 85) was not accompanied by pain. However, when 30 cc. of the aspirate obtained at *A* was reintroduced into the stomach two minutes later at *J*, severe pain appeared in six minutes (*K*), quickly becoming intolerable (*L*). Its intensity may be inferred from the marked increase in the amplitude of the respiratory excursion. This is a phenomenon which we have noted in this patient only. The stomach was immediately emptied (*M*) of 30 cc. of gastric juice (free acidity, 62); four minutes later (*N*) the pain was approximately 50 per cent better; six minutes later (*O*) 4 Gm. of calcium carbonate was given in 20 cc. of water. The pain disappeared completely within six minutes (*Q*) after the injection of the alkali. The experiment shows clearly the relief from ulcer distress by continuous aspiration of the stomach, and the production of excruciating pain by the introduction of the physiologic irritant, the patient's own gastric juice containing a rather high free acidity. This distress was relieved by emptying the stomach and injecting alkali. It was not accompanied by any significant change in gastric motility or intragastric pressure.

The following protocol, obtained in the study of a case of duodenal ulcer, shows that the pain-producing mechanism of ulcer is not desensitized by the injection of atropine sulphate.

CASE 2.—2:45 p. m.: One milligram of atropine sulphate was injected intravenously. No pain was present.

2:50: Two hundred cubic centimeters of a 0.5 per cent solution of hydrochloric acid was injected.

2:52: The pain came on suddenly.

2:55: Severe pain was present. The patient cried, doubled over with pain and rocked back and forth in her chair. The pulse rate was 122.

3:00: The patient complained of faintness; the pain continued to be severe, and the patient had to be supported in a chair. The stomach was aspirated and washed with 200 cc. of water.

3:05: The pain was somewhat relieved; washing of the stomach was continued with 200 cc. of water.

3:10: The pain was only slight; the washing with 200 cc. of water was continued.

3:15: The pain ceased; the washings showed no free acid.

The severity of the pain is noteworthy. Smith, Paul and Fowler [29] have shown that spontaneous ulcer distress may be relieved rather promptly by the intravenous injection of atropine sulphate. The mechanism of this relief will be discussed later. In this experiment, however, the production of excruciating pain by means of the acid test immediately

after the administration of atropine sulphate intravenously certainly shows that the relief described is not due to desensitization of the pain-producing mechanism.

The following protocol from another case of duodenal ulcer illustrates the same point. A kymographic record was made but is not reproduced here.

CASE 3.—2: 45-4: 00 p. m.: There was a normal gastric hunger period without pain.

4: 23: The stomach was emptied; 20 cc. of gastric juice was obtained; the free acidity was 68; total, 77.

4: 25-4: 38: Two hundred cubic centimeters of a 0.5 per cent solution of hydrochloric acid was administered by tube.

4: 42: Pain in the back appeared.

4: 46: Typical epigastric pain appeared.

4: 51: One milligram of atropine sulphate was injected intravenously.

5: 10: The steady continuous pain became more severe.

5: 20-5: 24: The pain remained the same. Two hundred cubic centimeters of tenth-normal solution of sodium hydroxide was given by tube.

5: 28: There was intense nausea with emesis of about 100 cc. of clear liquid; this was lost. The pain was completely relieved.

In this experiment the atropine sulphate was given during the period of pain with no relief whatsoever. On the other hand, relief came quite promptly after the introduction of alkali.

The kymographic tracing shown in figure 2 illustrates the failure of atropine sulphate to give relief and the direct relationship between pain and free acidity. The spontaneous distress present at the beginning of the tracing (*A*, 11: 15 a. m.) disappeared at *B* (11: 20) after the stomach had been aspirated at *A*, yielding a free acidity of 45. The distress recurred at *C* (11: 30), and 20 cc. of gastric content, free acidity, 60, was obtained. At *D* the pain was about half gone, and at *E* (11: 43) it had completely disappeared. Continuous aspiration of 45 cc. of gastric juice, free acidity, 64, from *E* to *F* (11: 43 a. m. to 12: 30 p. m.) kept the patient free from distress for forty-seven minutes. One milligram of atropine sulphate was given intravenously at *G* (12: 32), and at the same time 35 cc. of the gastric juice with a free acidity of 64 aspirated at *F* was reintroduced. Severe pain appeared in three minutes (*H*), becoming intense three minutes later, as the increase in the amplitude of the respiratory excursion shows. It is noteworthy that here again the stimulus employed was the perfectly physiologic one of the patient's own gastric juice. The distress subsided spontaneously twelve minutes later at *K* (12: 50). At *L* only 10 cc. of gastric juice, free acidity 60, was found in the stomach. Sixty cubic centimeters of a 0.5 per cent solution of hydrochloric acid was then introduced, agonizing pain resulting in three minutes. The pain was unbearable at *N*. The

stomach was aspirated at *O* (1:02) and yielded 90 cc., free acidity 95. Four grams of calcium carbonate was given at *P* (1:05), complete relief being obtained in seven minutes (*R*). Samples of gastric content showed no free acid. In this experiment atropine sulphate failed to prevent the production of pain by the physiologic medium of the patient's own gastric juice or by the artificial stimulus of a 0.5 per cent solution of hydrochloric acid.

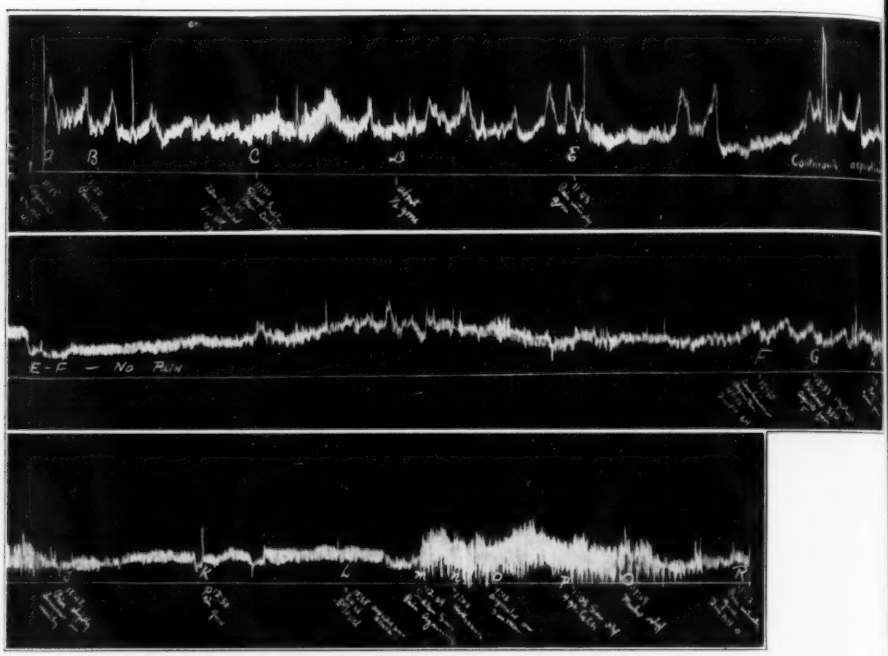

Fig. 2.—Kymographic tracing from a case of active duodenal ulcer showing: (1) that the intravenous injection of atropine prevented the appearance of severe ulcer pain following the reinjection of the normal acid gastric content, and (2) that the severe pain produced by the injection of a solution of hydrochloric acid was relieved by emptying the stomach and administering calcium carbonate.

Bauer, Salter and Aub,[50] in studying the effect of the intravenous administration of calcium chloride on pain of muscular origin, noted that the injection failed to relieve certain cases of duodenal ulcer pain. This is significant, although we have induced relief frequently as in the following protocol from a case of duodenal ulcer:

50. Bauer, Walter; Salter, W. T., and Aub, J. C.: Studies of Calcium and Phosphorus Metabolism: X. The Use of Calcium Chloride to Relieve Peristaltic Pain, J. A. M. A. **96**:1216 (April 11) 1931.

CASE 4.—2:47 p. m.: The stomach was emptied, and yielded 30 cc. of clear liquid with a free acidity of 59; total, 88.

2:53: One milligram of atropine sulphate was injected intravenously.

3:21: Two hundred cubic centimeters of 0.5 per cent solution of hydrochloric acid was given by tube. The pain which appeared during the injection was quite severe and typical.

3:35: One gram of calcium chloride was injected intravenously.

3:44: The pain was still present but much less severe.

3:50: There was some nausea; the pain was still present.

3:53: The pain was nearly gone; the nausea persisted.

4:03 to 4:06: Two hundred cubic centimeters of a 0.5 per cent solution of hydrochloric acid was given by tube.

4:10: The nausea persisted.

4:20: The nausea decreased.

4:30: The nausea was gone.

4:45: Twenty cubic centimeters of gastric content was aspirated; the free acidity was 78; total, 82.

5:10: Two hundred cubic centimeters of a 0.5 per cent solution of hydrochloric acid was given.

6:12: The stomach was aspirated and yielded 190 cc. of a clear liquid; the free acidity was 91; total, 96. There was no pain.

Here again atropine sulphate failed to desensitize the pain-producing mechanism, but the severe pain produced by the injection of acid decreased quite rapidly and promptly after the administration of calcium chloride. It is important to note that this relief was accompanied by nausea, and that nausea persisted after the pain had been relieved. The injection of 200 cc. of a 0.5 per cent solution of hydrochloric acid did not produce pain, and the nausea continued. The third injection of acid also failed to produce pain. The probable mechanism involved in this phenomenon will be discussed later.

Figure 3 shows the kymographic study of a similar experiment. At *A* (3:05 p. m.) the stomach was aspirated, yielding 20 cc. of gastric juice, free acidity, 42. Moderate pain appeared at *B* (3:45) and became excruciating at *C*, *D* and *E*. The stomach was aspirated between *E* and *G*, yielding a free acidity of 64. The intravenous administration of 10 cc. of a 10 per cent solution of calcium chloride ending at *G* gave prompt but very brief relief. At *J* (4:02) 95 cc. of a 0.3 per cent solution of hydrochloric acid was injected. The free acidity was 65. At *L* (4:07) the patient was again doubled up with pain which continued, quickly becoming intolerable (*M*) until the stomach was aspirated (*N*), yielding 95 cc. of contents, free acidity, 64. At *O* the pain was half gone. From *P* to *S* continuous aspiration yielded 40 cc. of gastric content, free acidity, 45. At *T* 90 cc. of the gastric juice aspirated at *N*, free acidity, 64, was reinjected. Pain reappeared at *U*, rapidly becoming severe; it was momentarily decreased by the injection of 1 mg. of atropine sul-

phate intravenously at V (4:39), but quickly became excruciating again at X (4:43), the patient writhing in pain from X to Y. At Y (4:45) the stomach was aspirated, 70 cc. of gastric content with a free acidity of 60 being obtained. Two grams of sodium bicarbonate in 30 cc. of water was given at Z, with complete relief eleven minutes later, at Z_1. Here one notes that both calcium chloride and atropine sulphate

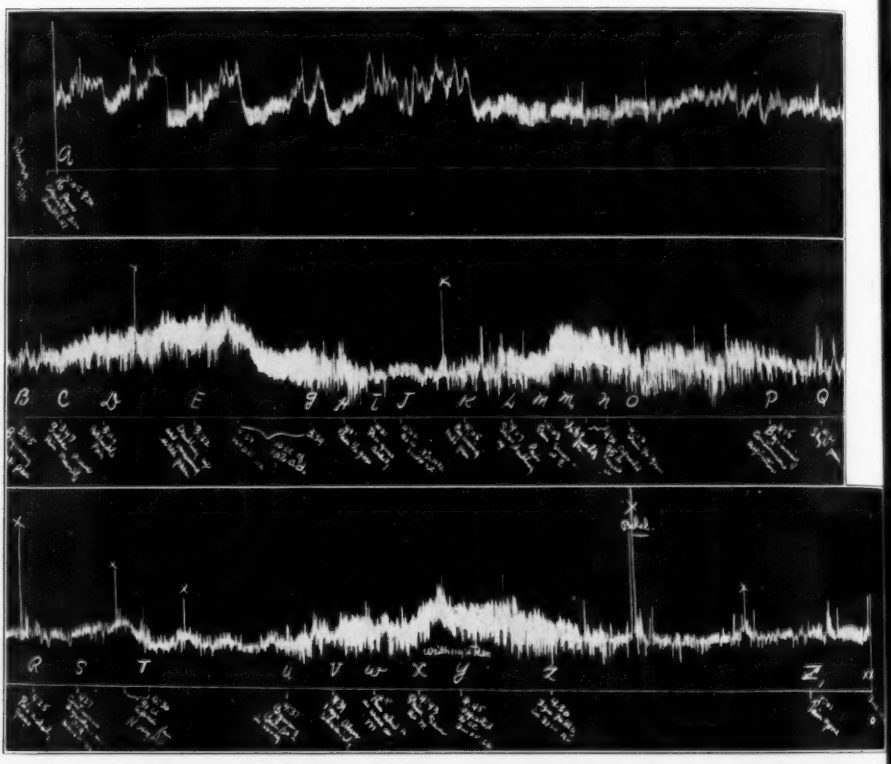

Fig. 3.—Kymographic tracing from a case of active gastric ulcer showing: (1) transitory relief from ulcer pain by the intravenous injection of calcium chloride; (2) the failure of atropine sulphate to relieve distress induced by the reinjection of the patient's own gastric juice, and (3) relief from emptying the stomach and administering sodium bicarbonate.

failed to desensitize the pain-producing mechanism, and again that excruciating pain was produced by the reintroduction of the normal physiologic irritant, the patient's own gastric juice. At XX samples of gastric content contained no acidity.

Similar studies have been made in a case of carcinomatous gastric ulcer with a high free acidity, as in the following protocol:

CASE 5.—2:07 p. m.: There was a constant dull pain.

2:20: Ten cubic centimeters of the gastric content was aspirated; the free hydrochloric acid was 38; total, 83.

2:35: The pain grew more severe.

3:00: The pain continued unchanged. One gram of calcium chloride was given intravenously.

3:04-3:08: The pain was nearly gone.

3:17: A mild dull pain continued.

3:18: One milligram of histamine hydrochloride was given subcutaneously. The stomach was aspirated, yielding 10 cc. of gastric content with a free acidity of 40; total, 75.

3:30: The pain became severe; headache developed.

3:35: The pain increased; there was emesis of 90 cc. of liquid with thick mucus. The free acidity was 37; total, 55.

3:43: The patient writhed and rolled in great agony.

3:44: Four grams each of sodium bicarbonate and calcium carbonate were given by mouth.

3:48: The pain decreased; the patient stated: "The worst of it is gone."

3:54: The pain was slighter than at any time in the afternoon.

The distress in this instance disappeared for a brief time after the administration of calcium chloride and then recurred. One milligram of histamine hydrochloride was given subcutaneously; this was followed by an increase in the pain, so that twenty-five minutes later the patient was writhing and rolling about in agony. Four grams each of calcium carbonate and sodium bicarbonate were given by mouth with almost complete relief in ten minutes.

Figure 4 is a kymographic tracing of the same patient. At *A* (2:18 p. m.) type I hunger contractions were present. At *B* the stomach was emptied of 20 cc. of the gastric content, free acidity 72, total 92. Typical pain appeared at *C* (2:58) and increased until at *F* (3:08) the patient writhed in agony. From 3:09 to 3:12, 10 cc. of a 10 per cent solution of calcium chloride was given intravenously. At *G* the pain seemed to be 75 per cent relieved, but it quickly increased again at *H* (3:18), and at *I* the patient was again writhing. (The irregular fluctuations in the curve are due to changes in position, etc.) At *J* 1 mg. of atropine sulphate was given intravenously, but agonizing pain continued at *K*, the patient exclaiming, "God, it does hurt me!" The pain continued at *L*. At *M* the stomach was emptied, 140 cc. of clear gastric juice with a free acidity of 45 being obtained. This was followed in eight minutes by 75 per cent relief of the pain present at *N*. It increased slightly at *O* but at *Q* was completely gone. One hundred and thirty cubic centimeters of the gastric content with a free

acidity of 45 was then reintroduced at *R* (5:00 to 5:03) with recurrence of the pain twenty minutes later at *S*. The stomach was emptied (*T*, 5:25), 140 cc. of blood-tinged liquid with a free acidity of 40 being obtained, but the pain was more severe five minutes later at *U*, when

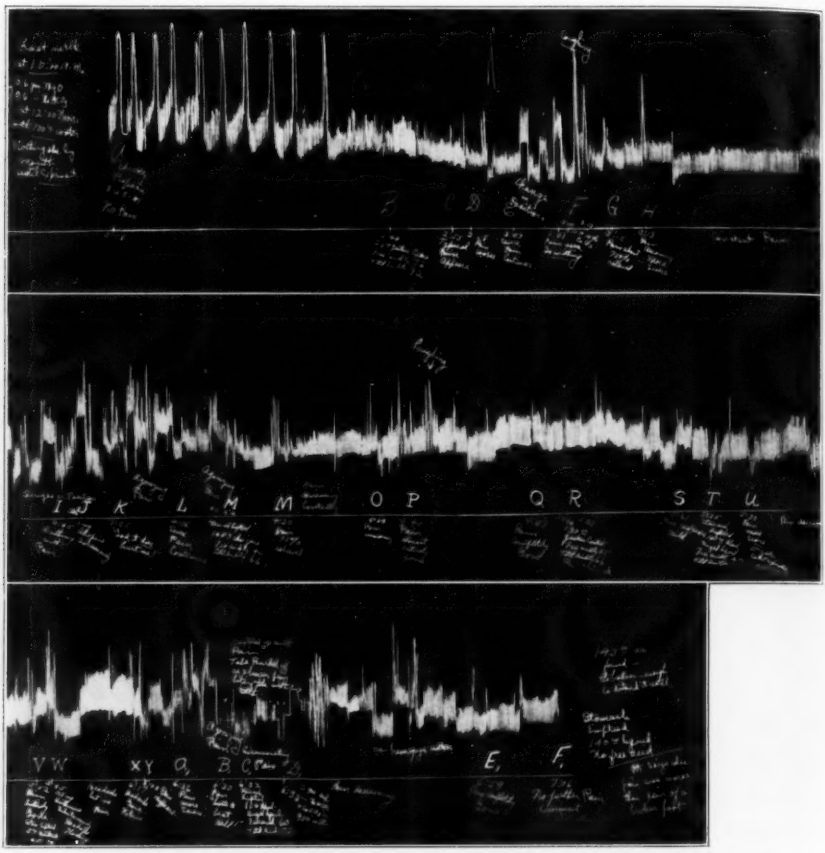

Fig. 4.—Kymographic tracing from a case of carcinomatous gastric ulcer showing: (1) the relation of pain to gastric acidity; (2) slight transitory relief from the intravenous injection of calcium chloride; (3) no relief from the intravenous injection of atropine sulphate; (4) relief from emptying the stomach; (5) pain attributed to gastric secretion in response to the subcutaneous injection of histamine hydrochloride, and (6) relief from alkali medication.

5 cc. of gastric content with a free acidity of 45 was removed. The pain steadily decreased from *U* to *V*, disappearing entirely at *V*, at which

time only 5 cc. of content, free acidity of 45, total 66, was found in the stomach. The free acidity present was adequate for the production of pain, as has just been shown (*R* to *U*). The explanation for the relief from pain in spite of the high free acidity is probably to be found in the very small amount (5 cc.) of gastric content present. It may be shown roentgenologically that in the empty stomach, collapsed by its own musculature and by intra-abdominal pressure, the very few cubic centimeters of gastric content present is located in the fundic portion just below the air bubble. Large quantities of gastric content are required if the surface of the lesion is to be bathed by acid chyme, and pain produced. One-half milligram of histamine was then given sub-

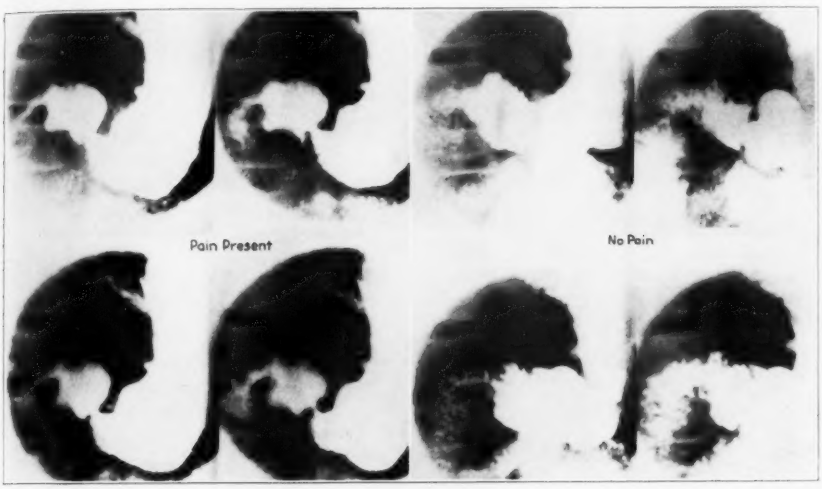

Fig. 5.—Roentgenograms made in a case of benign gastric ulcer.

cutaneously at *W*; headache and flushing of the face appeared almost at once. Pain appeared twenty-seven minutes later at *Y*, becoming quite severe at A_1 and agonizing at B_1, when the patient exclaimed "It hurts to beat hell!" At C_1 the pain was so excruciating that the patient, in clinching and grinding his teeth, shut off the tube connected with the manometer and interfered with the recording of intragastric pressure. Two grams each of calcium carbonate and sodium bicarbonate were given at D_1 with a gradual decrease in pain from D_1 to E_1, at which time it disappeared entirely.

In this observation of the behavior of the excruciating pain seen in a patient with a carcinomatous ulcer associated with a high gastric acidity, it may be seen that the pain was only temporarily allayed by the intravenous injection of calcium chloride, that it was not influenced

by the intravenous injection of 1 mg. of atropine sulphate, but that it was relieved by emptying the stomach and also by neutralizing the free acidity. The patient could be kept free from distress by maintaining continuous neutralization of the free acidity. Agonizing pain was pro-

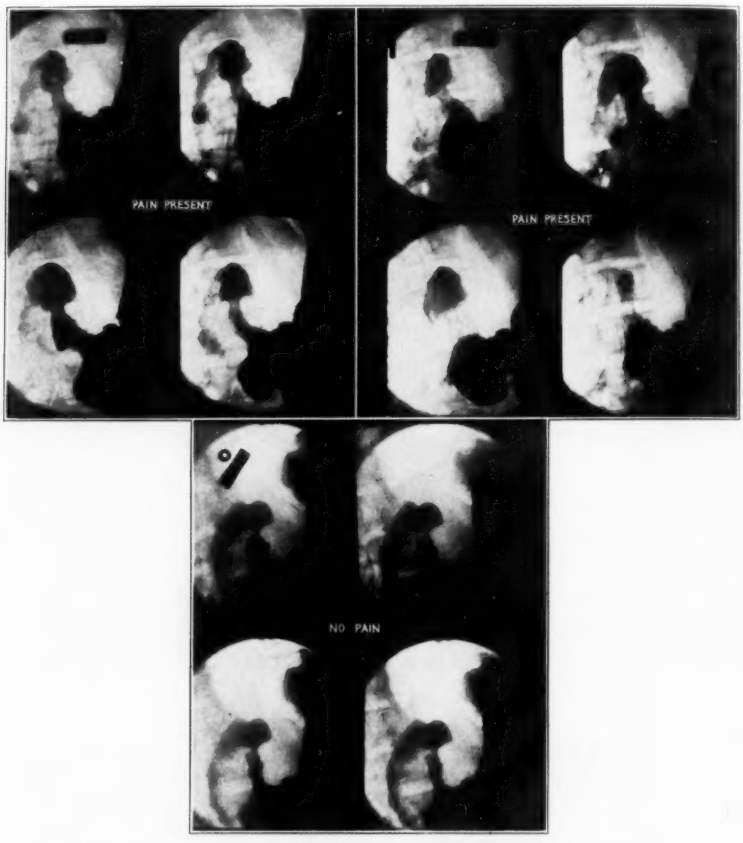

Fig. 6.—Roentgenograms made in a case of carcinomatous gastric ulcer.

duced by the injection into the stomach of the normal physiologic irritant, *the patient's own gastric juice,* or also by increasing the amount of gastric secretion by means of the injection of histamine hydrochloride.

The kymographic method as employed in our experiments provides a record of intragastric tension and therefore of gastric tonus as well as gastric motility, but it does not provide information with regard to the pylorus or the duodenal bulb. These regions were studied care-

fully roentgenologically [13] in 1926, as has been mentioned, and evidence was obtained that ulcer pain is not due to pylorospasm, spasm of the gastric antrum or increased pressure in the antrum. However, in view of the criticism of Hurst [28b] further observations were made.

The roentgenologic appearance of the stomach in the presence of pain and again in its absence in a case of benign gastric ulcer is illustrated in figure 5. The second series of exposures was made thirty minutes after the first, and at a time when the pain had disappeared as the result of the administration of an alkali. Fluoroscopic studies of the stomach during the presence of pain following the administration of a preparation of barium sulphate made up in a 0.5 per cent solution of hydrochloric acid corroborated the roentgenologic findings reproduced here. The stomach emptied well during pain, thus proving that the pain was not due to pylorospasm. There was no spasm in the gastric antrum, in the body of the stomach or in the duodenal bulb.

Similar observations made in the case of carcinomatous gastric ulcer previously mentioned are presented in the series of roentgenograms shown in figure 6, illustrating and confirming the fluoroscopic studies. The ulcer crater on the lesser curvature may be noted. The prepyloric deformity was present constantly, regardless of the acidity of the gastric content and regardless of the presence or absence of pain. It varied somewhat in its configuration with different phases of filling, but this variation was independent of any variation in the pain, as may be seen from a study of the illustration. Eight exposures of the antrum were taken during the presence of pain induced by the administration of acid solution of barium sulphate and four more thirty or forty minutes later after the pain had been relieved by alkali medication. In some the antrum is well filled out; in others, it is almost empty. The pylorus is open in nearly all and the duodenal bulb well filled. The same variations occur regardless of the presence or absence of pain. The patient was operated on and a partial gastrectomy performed. Gross and microscopic examination of the gastric antrum revealed diffuse carcinomatous infiltration throughout the lymphatic vessels of the submucosa with marked thickening and rigidity of the tissue. The constant prepyloric deformity noted roentgenologically was thus attributable to anatomic change rather than to spasm. In these observations it is quite clear that the pain was not due to spasm of the body of the stomach, of the antrum, of the pylorus or of the duodenal bulb, and there is no evidence of a constricting wave of gastric peristalsis which might have produced an increase in the intragastric tension in the pyloric segment not transmitted to the main segment, as suggested by Hurst.

COMMENT

A complete discussion of the subject of visceral pain can scarcely be attempted in this paper. The reader is undoubtedly familiar with the

original work of Lennander,[45] Ross,[51] Mackenzie,[52] Hurst [9] and others. Of the numerous studies on this subject in recent years those of Soma Weiss and Davis,[53] Pratt, Golden and Rosenthal,[54] Rudolf and Smith,[55] Davis, Pollock and Stone [56] and particularly the monographs of Lemaire,[57] Morley [46] and Capps [58] are of great interest. In our work, however, ulcer pain has been accepted as a fact. The lesion is known to be present; the nerve supply is abundant; and in some way an adequate stimulus is applied to some nerve mechanism with consequent perception of pain. In this study our attention has been centered on the manner in which pain arises, on its site of origin, and on the nature of the adequate stimulus, rather than on the type of nerve or nerve ending excited, the pathway of the pain or the manner in which it is referred.

The Source of Ulcer Pain.—In view of the many and contradictory theories which have been advanced to explain ulcer pain, it is important to determine first, if possible, the site of origin of the pain. Does it arise in or adjacent to the ulcer itself or in some more distant part of the stomach or duodenum? Hurst,[28a] Smith, Paul and Fowler [29] and others have considered the source to be the normal tissue of the wall of the pyloric antrum and the adequate stimulus the increased tension resulting from increased intragastric pressure. Ginsburg, Tumpkowsky and Hamburger,[14] Carlson [15] and Christensen,[36] on the other hand, while agreeing that the site of origin is the normal musculature, have considered peristalsis to be the adequate stimulus. The difference between the pain of ulcer and the "hunger pang" of a normal stomach was attributed apparently to the hypersensitivity of the whole region induced in the former instance by the more or less distant inflammatory lesion. A careful consideration of all the evidence, however, indicates

51. Ross, James: On the Segmental Distribution of Sensory Disorders, Brain **10**:333, 1888.

52. Mackenzie, James: Remarks on the Meaning and Mechanism of Visceral Pain, Brit. M. J. **1**:1449 and 1523, 1926.

53. Weiss, Soma, and Davis, David: The Significance of the Afferent Impulses from the Skin in the Mechanism of Visceral Pain, Am. J. M. Sc. **176**:517, 1928.

54. Pratt, J. H.; Golden, L. A., and Rosenthal, Joseph: The Psychalgias: A Study by Means of the Novocaine Skin Test of Their Frequency and Characteristics, Tr. A. Am. Physicians **46**:313, 1931.

55. Rudolf, R. D., and Smith, A. G.: Observations on Visceral Pain, Tr. A. Am. Physicians **45**:264, 1930.

56. Davis, Loyal; Pollock, L. J., and Stone, T. T.: Visceral Pain, Surg., Gynec. & Obst. **55**:418 (Oct.) 1932.

57. Lemaire, A.: Le problème de la sensibilité viscérale et l'anesthésie de splanchnalgies, Paris, Pressess Universitaires de France, 1928.

58. Capps, J. A., and Coleman, George H.: An Experimental and Clinical Study of Pain in the Pleura, Pericardium, and Peritoneum, New York, The Macmillan Company, 1932.

that ulcer pain arises at the site of the ulcer. Our studies have shown that ordinarily ulcer pain is entirely independent of gastric peristalsis, gastric tone, intragastric pressure and pylorospasm, except as these influence gastric emptying and thereby affect the chemical nature of the fluid bathing the surface of the ulcer itself. In those cases in which the pain is intermittent or remittent, the waves of pain corresponding with the waves of peristalsis noted kymographically, it seems probable that here also the pain is not due to changes in the tension of the muscles in the normal stomach but rather to direct mechanical irritation of the lesion itself either by a transmitted tug or by the further advance of the contraction to the site of the ulcer. The direct observations of Dragstedt and Palmer,[49] in the patient operated on under local anesthesia as described, have shown that direct irritation of a sufficiently sensitive ulcer, such as may result from touching, rubbing, pinching, applying acid to the surface and circular muscular spasm, is extremely painful, whereas peristalsis and the application of similar trauma to other parts of the stomach are painless. It seems necessary to conclude, therefore, that *ulcer pain arises at the site of the lesion.*

Ulcer Sensitivity.—Before considering the phenomenon of ulcer sensitivity or irritability in detail, it seems advisable to review our knowledge of the etiology and pathogenesis of ulcer, giving particular attention to the rôle of acid gastric juice. Alvarez [59] recently published an excellent résumé of the subject with an extensive bibliography.

In 1926, the literature dealing with the alleged incidence of peptic ulcer associated with complete achlorhydria was reviewed [60] with the conclusion that there were no well documented cases on record. Many of the older writers had accepted a single Ewald or a single fractional test meal as satisfactory evidence of the inability of the stomach to secrete free hydrochloric acid. It was shown, however, that several analyses must be made before a diagnosis of achlorhydria can be considered as established. Achlorhydria proved by a test with histamine is usually accepted as satisfactory, but recently the conclusive value of this test has been properly questioned by Gaither,[61] Comfort and Osterberg [62] and Klumpp and Bowie.[63] We have also noted instances in which a test with histamine was reported as showing no free acid,

59. Alvarez, W. C.: Light from the Laboratory and the Clinic on the Causes of Peptic Ulcer, Am. J. Surg. **18**:207 (Nov.) 1932.

60. Palmer, W. L.: The Mechanism of Pain in Gastric and Duodenal Ulcers: I. Achlorhydria, Arch. Int. Med. **38**:603 (Nov.) 1926.

61. Gaither, E. H.: Diagnostic Value of Secretory Function in Gastric Disease: Various Methods Studied and Compared, Ann. Int. Med. **5**:992, 1932.

62. Comfort, M. W., and Osterberg, A. E.: Gastric Secretion After Stimulation with Histamine, J. A. M. A. **97**:1141 (Oct. 17) 1931.

63. Klumpp, T. G., and Bowie, M. A.: Studies on Gastric Secretion, J. Clin. Investigation **12**:1 (Jan.) 1933.

whereas a second test showed its presence in normal quantity. Neither conclusive nor even fairly acceptable evidence, therefore, of the presence of complete achlorhydria in typical chronic ulcer has yet been reported. Berg [64a] referred to a case of duodenal ulcer and achlorhydria following gastro-enterostomy, but did not give the evidence. Gutzeit [64b] stated that he found a gastric ulcer by gastroscopic examination in a patient with pernicious anemia and achylia proved by a test with histamine, but the lesion was seen only once and the patient had no symptoms of ulcer.[65] Hurst [28c] made the statement, "There is thus no evidence that an ulcer ever develops in the stomach or duodenum in the absence of free hydrochloric acid." This is extremely significant, for Vanzant, Alvarez, Eustermann, Dunn and Berkson,[66] in their extensive studies on gastric secretion, found true achlorhydria present in 10.8 per cent of males of all ages above 25, and in 13.8 per cent of all females above 20. These results are quite in accord with the 13 per cent incidence of anacidity reported by Lerman, Pierce and Brogan.[67] *If free hydrochloric acid plays no rôle in the genesis of ulcer, the incidence of achlorhydria in ulcer should be from 10 to 13 per cent instead of 0.*

It is furthermore highly significant that ulcer occurs only in those portions of the gastro-intestinal tract exposed to peptic activity: the lower part of the esophagus, the stomach and the proximal portion of the duodenum. Following operative procedures which bring the jejunum into contact with unneutralized acid, lesions may develop in the jejunum, or if the anastomosis is lower, in the ileum or colon.

The ulcers of Meckel's diverticulum, studied carefully by Aschner and Karelitz,[68] Lindau and Wulff,[69] Matthews and Dragstedt [70] and others are extremely important. These lesions occur in the intestinal mucosa lining the neck of the diverticulum, and are associated with the presence in the sac of gastric mucosa secreting free hydrochloric acid. The experimental production of these lesions by Dragstedt and Matthews,[70] to be mentioned again later, is a conclusive demonstration of the rôle of hydrochloric acid in the pathogenesis of these ulcers.

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64. (*a*) Berg, H. H.: Roentgenuntersuchungen am Innenrelief des Verdauungskanals, ed. 2, Leipzig, Georg Thieme, 1931, p. 149; (*b*) ibid., p. 321.

65. Gutzeit, Kurt: Personal communication to the authors.

66. Vanzant, F. R.; Alvarez, W. C.; Eustermann, G. B.; Dunn, H. L., and Berkson, Joseph: The Normal Range of Gastric Acidity from Youth to Old Age, Arch. Int. Med. **49**:345 (March) 1932.

67. Lerman, J.; Pierce, F. D., and Brogan, A. J.: Gastric Acidity in Normal Individuals, J. Clin. Investigation **11**:155, 1932.

68. Aschner, P. W., and Karelitz, S.: Peptic Ulcer of Meckel's Diverticulum and Ileum, Ann. Surg. **91**:573, 1930.

69. Lindau, Arvid, and Wulff, Helge: The Peptic Genesis of Gastric and Duodenal Ulcer; Especially in the Light of Ulcers in Meckel's Diverticulum and the Post-Operative Ulcers in the Jejunum, Surg., Gynec. & Obst. **53**:621, 1931.

70. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **55**:265, 1932.

Pathologically, the work of Moskowitz,[71] Konjetzny,[72] Puhl,[73] Aschner and Grossman[74] and others has quite altered the time-honored concept of the pathogenesis of ulcer. It has been shown by these workers that gastritis and duodenitis are constantly associated with ulcer, and that occasionally they alone may produce the ulcer syndrome. Various stages of transition from gastritis to ulcer have been demonstrated. Konjetzny and Puhl favor the view that the same inciting agent is present in both of these lesions. They believe that it is a toxic or infectious process and deny the rôle of gastric acidity.

Büchner[75] and his pupils, on the other hand, while confirming the work of Konjetzny as regards the relationship between gastritis and ulcer, present evidence that both are of peptic origin. The layer of "fibrinoid necrosis" described by Askanazy[76] and invariably present in ulcer is considered by Büchner as the typical picture of corrosive necrosis. The small lesions of Konjetzny's ulcerative gastritis have been shown by Büchner to have a similar histologic structure. Furthermore, Büchner and his pupils have succeeded in producing this picture of ulcerative gastritis experimentally in cats by the injection of acid into the stomach, and also in rats by stimulation of gastric secretion with histamine during periods of fasting. In the latter experiments there were produced not only the erosions and the small, although grossly visible, lesions of ulcerative gastritis, but small ulcers of the prostomach extending occasionally to the muscularis propria. A somewhat similar observation was reported by Silbermann,[77] who noted the erosions of ulcerative gastritis in the stomach of dogs following sham feeding experiments. This work was confirmed by Büchner and attributed to the effect of undiluted and unneutralized acid on the mucosa.

The first satisfactory production of ulcer in a sense was that inadvertently obtained by surgeons in human material by various types

71. Moskowitz, Ludwig: Zur Histologie des Ulcusbereiten Magens, Arch. f. klin. Chir. **122**:444, 1922.

72. Konjetzny, G. E.: Die entzündliche Grundlage der typischen Geschwürsbildung im Magen und Duodenum, Ergebn. d. inn. Med. u. Kinderh. **37**:184, 1930.

73. Puhl, H.: Ueber die Bedeutung entzündlicher Prozesse für die Entstehung des Ulcus ventriculi et duodeni, Virchows Arch. f. path. Anat. **260**:1, 1926; Zur Pathologie und Klinik des Ulcus duodeni, Deutsche Ztschr. f. Chir. **207**:202, 1927; Ueber die Entstehung und Entwicklung des Magen-Duodenal-Geschwürs, Arch. f. klin. Chir. **158**:1, 1930.

74. Aschner, P. W., and Grossman, Sidney: Gastritis and Duodenitis in Relation to the Ulcer Problem, Tr. Am. Gastro-Enterol. A., 1932, p. 102.

75. Büchner, F.: Die Pathogenese der peptischen Veränderungen, Jena, Gustav Fischer, 1931.

76. Askanazy, M.: Ueber Bau und Entstehung des chronischen Magengeschwürs, so wie Soorpilzbefunde in ihm, Virchows Arch. f. path. Anat. **234**:111, 1921; **250**:370, 1924.

77. Silbermann, I. S.: Experimentelle Magen-Duodenal-Ulcuserzeugung durch Scheinfütterung nach Pavlov, Zentralbl. f. Chir. **38**:2385, 1927.

of gastro-enterostomy with ligation or resection of the pylorus. The incidence of jejunal ulcer following this procedure was high.[28d] In 1923, Mann and Williamson [78] found experimentally that transplantation of the bile and pancreatic ducts to the terminal ileum in the dog resulted in the formation of ulcers in nearly all of the animals. This observation has been abundantly repeated and confirmed, in various types of so-called "duodenal drainage operations," by Morton,[79] McCann,[80] Matthews and Dragstedt,[70] Gallagher and Palmer [81] and others. Similarly, it has been observed that complete biliary obstruction results experimentally in the formation of ulcers in about 60 per cent of the animals, as stated by Berg and Jobling,[82] Bollman and Mann [83] and Kim and Ivy.[84] Elman and Hartmann [85] reported the formation of ulcers in six dogs in which the pancreatic juice was drained away for thirteen days or more, but Owings and Smith [86] and Berg and Zucker [87] were unable to confirm this observation. Dragstedt,[88] however, in his extensive studies on dogs with total pancreatic fistulas has found it very difficult to keep animals alive for more than a week because of the rapidity with which duodenal ulcers arise, perforate and cause death from peritonitis. When such animals are fed alkali regularly, it is possible to prevent the formation of ulcers for as long as six months. Apparently any disturbance of the normal mechanism for the neutralization of acid in the duodenum will result in the formation of ulcers in a very high percentage of the experiments. The lesions, frequently hemorrhage, invade adjacent organs and

78. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409, 1923.

79. Morton, C. B.: Observations on Peptic Ulcer: I. A Method of Producing Chronic Gastric Ulcer, Ann. Surg. **85**:207, 1927.

80. McCann, J. C.: Experimental Peptic Ulcer, Arch. Surg. **19**:600 (Oct.) 1929.

81. Gallagher, W. J., and Palmer, W. L.: Experimental Jejunal Ulcer: The Relative Importance of Mechanical and Chemical Factors, Proc. Soc. Exper. Biol. & Med. **30**:468, 1933.

82. Berg, B. N., and Jobling, J. W.: Biliary and Hepatic Factors in Peptic Ulcers, Arch. Surg. **20**:997 (June) 1930.

83. Bollman, J. L., and Mann, F. C.: Peptic Ulcer in Experimental Obstructive Jaundice, Arch. Surg. **24**:126 (Jan.) 1932.

84. Kim, M. S., and Ivy, A. C.: The Prevention of Experimental Duodenal Ulcer by Feeding Neutral Gastric Mucin, J. A. M. A. **97**:1511 (Nov. 21) 1931.

85. Elman, R., and Hartmann, A. F.: Spontaneous Peptic Ulcers of Duodenum After Continued Loss of Total Pancreatic Juice, Arch. Surg. **23**:1030 (Dec.) 1931.

86. Owings, J. C., and Smith, I. H.: The Etiology of Duodenal Ulcers, Proc. Soc. Exper. Biol. & Med. **29**:833 (April) 1932.

87. Berg, B. W., and Zucker, T. F.: Comparative Frequency of Peptic Ulcers After Deprivation of Bile and Pancreatic Juice, Proc. Soc. Exper. Biol. & Med. **30**:330 (Dec.) 1932.

88. Dragstedt, L. R.: Personal communication to the authors.

often perforate with resulting death from peritonitis. They are not thrombotic or infarctive in origin, for Mann has shown conclusively that the process is an invasive one; that it begins in the mucosa and extends into the deeper layers and thus increases in size. It should be noted here, as pointed out by Büchner,[89] that in human material also the ulcerative lesion may *invade* adjacent organs—a process which cannot be explained by thrombosis or embolism with subsequent infarction. The acid genesis of these ulcers is perhaps most conclusively proved by the experimental production of ulcers of Meckel's diverticulum by Matthews and Dragstedt.[70] Here the acid gastric juice draining from a Pavlov pouch into a loop of ileum results in the formation of ulcers. Continued neutralization of the acid allows the lesions to heal and prevents the formation of new ones.[90] *These experiments show clearly that unneutralized gastric juice is able to initiate in normal living tissue a localized ulcerative process and that it is also able to bring about the extension and chronicity of the lesion so induced.*

In view of the foregoing clinical, pathologic and experimental considerations, it is apparent that peptic ulcer occurs only in association with acid gastric juice, that the various stages from ulcerative gastritis to the formation of callous ulcer have been described anatomically, that all of these stages have been reproduced experimentally by various methods which increase the exposure of the mucosa to acid gastric chyme, and that in normal tissue acid gastric juice alone is able to initiate, maintain and extend an ulcer. This brings us, then, to a consideration of the process which renders an ulcer sensitive to otherwise inadequate stimuli. There is evidence that this is due to the inflammatory process itself, even though Singer and Palmer[91] were unable to establish a relationship between the various degrees of inflammation and the sensitivity of ulcers. This may have been due in part to inability to find a satisfactory means of measuring degrees of inflammation.

The clinical evidence of such a relationship is quite definite. The first symptomatic signs of subsidence of the inflammatory process and therefore of healing should be and are a cessation of spontaneous distress followed by failure of the previously adequate stimuli to produce pain. During the first few days of antacid ulcer therapy, and also during the early days of a spontaneous remission, during which time the reparative healing processes are apparently in ascendancy, the sensitivity to acid more or less rapidly diminishes, more *time* is required for the production of pain, and the resulting pain becomes less and less severe.[92]

89. Büchner,[75] p. 4.

90. Matthews, W. B.: Personal communication to the authors.

91. Singer, Harry, and Palmer, W. L.: Unpublished observations.

92. Palmer, W. L.: The Value of Acid Neutralization in the Treatment of Gastric and Duodenal Ulcers, Arch. Int. Med. **46**:165 (Aug.) 1930.

Coincidentally the epigastric soreness and the rigidity of the rectus muscle disappear. Berg [64b] has shown roentgenologically that these phenomena occur long before the ulcer crater closes. We have found that in these stages of partial to complete healing, the lesion is insensitive to acid and furthermore desensitization occurs more rapidly on an antacid than on an acid-producing regimen.[92] These are the results to be expected, if acid gastric juice is responsible, as has been suggested, for the initiation and continuation of the lesion, because prolonged neutralization of the acid should allow granulation tissue to fill in, mucosal cells to bridge the gap, and the ulcer to heal.

Further evidence that the enhanced irritability of the ulcer is due to the continued action of the noxious agent, acid gastric juice, is to be found in a case of gastric carcinoma previously described.[13c] In this instance, free hydrochloric acid was present in normal amounts. The spontaneous pain was severe; it could be produced in almost agonizing form by the "acid test," and it was completely relieved by antacid ulcer management (the usual Sippy regimen). With the continuation of treatment, not only did the patient remain free from spontaneous distress, but the "acid test" gradually became negative also, giving proof of the transformation from an acid-sensitive to an acid-insensitive lesion. The desensitization of the pain-producing mechanism seemed to result directly from the continued neutralization of the free acidity. This neutralization presumably protected the carcinoma from the digestive action of the gastric juice and thereby preserved over the surface of the lesion a sufficient layer of necrotic tissue to protect the mechanism of pain from the irritating effect of the acid used in the "acid test." This same phenomenon was observed in the case of carcinomatous gastric ulcer described in detail in the present paper. These observations are important because they constitute further evidence not only that acid gastric juice may destroy living tissue, but that it may, in the lesion produced, so lower the pain threshold that normally subthreshold stimuli become painful.

The importance of acid sensitization in ulcer was also clearly shown in the original studies [13d] of a case of gastrojejunal ulcer. In this instance gastric peristalsis was powerful but painless until an hour after the injection of 1.5 mg. of histamine hydrochloride subcutaneously. This produced a large volume of highly acid gastric secretion (free acidity of 100) which, in *time*, increased the irritability of both the motor and the sensory mechanisms of the stomach. Remittent pain appeared, the most intense pains corresponding with the peak of the gastric contractions, which had then increased in intensity. With continued neutralization of the free acidity, however, the pain gradually decreased and disappeared entirely even though the powerful peristaltic waves persisted.

It may be seen that this theory of sensitization as due to the continued destructive action of acid gastric juice is quite in accord with our concept of the etiology of ulcer. Free hydrochloric acid is responsible for the initiation and continuation of the inflammatory process and for the enhanced irritability of the tissue. When the lesion is protected from the destructive effect of the acid, the sensitivity disappears quickly, pain ceases, tenderness and rigidity disappear, and the ulcer heals.

The Adequate Stimulus.—Given a sensitive lesion, the production of pain depends on the presence of an adequate stimulus. It has been shown that this may be either mechanical or chemical. The early observations of Ginsburg, Tumpowsky and Hamburger [14] and of Carlson [15] showed definitely that under proper conditions gastric peristalsis itself may produce pain. Our own kymographic studies have been confirmatory. Dragstedt and Palmer [49] observed that direct mechanical irritation of an acutely inflamed ulcer, as by rubbing or pinching or local muscular contraction, produced severe pain. There can be no doubt, therefore, that purely mechanical stimuli may be entirely adequate. In the case of benign lesions, however, there is no evidence at present that an ulcer can occur and be sufficiently sensitive for the production of pain by mechanical stimulation without previous acid sensitization. With malignant lesions, on the other hand, the advance of the process is not dependent on continued peptic activity, and consequently enhanced irritability of the tissue may occur without the presence of free hydrochloric acid, as in the cases of gastric carcinoma with pain associated with a complete absence of free hydrochloric acid.[13e]

The evidence that free hydrochloric acid may be an adequate stimulus to the pain-producing mechanism may be summarized as follows:

1. When pain is present, a high degree of free hydrochloric acid is practically always found in the stomach.

2. The pain is relieved by emptying the stomach or by any measure which results in the neutralization of the gastric free acidity.

3. The pain may be relieved by emptying the stomach, and be made to reappear by reinjecting the acid chyme whereas the injection of gastric content in which the free acidity has been neutralized is not productive of pain.

4. Ulcer pain, typical in kind, location and severity, may be induced under suitable conditions by the injection into the stomach of dilute solutions of hydrochloric acid in perfectly physiologic concentrations (from 0.2 to 0.3 per cent). Dilute solutions of other acids and alkalis (tenth-normal solution of sodium hydroxide) have also evoked pain in highly sensitive lesions.

5. Ulcer pain may be induced by the injection of acid gastric juice from another patient or by stimulation of the patient's own gastric secretion by histamine.

6. In one instance, pain was produced by direct application of acid to the surface of the ulcer.[49]

It is impossible to estimate the relative rôles of these two forms of stimuli in the production of the usual ulcer pain. The acid factor must be present if pain is to ensue. On the other hand, an ulcer is seldom free from the effect of mechanical forces. It is significant, however, that a mechanical factor was demonstrated in Palmer's original work only in those cases in which the pain was wavelike, remittent or intermittent (9.5 per cent of the observations). Clinically, the most frequently encountered type of distress is not wavelike, but steady and continuous, just as is that usually seen following the introduction of acid into the stomach. Beams [38] noted, however, following the administration of amyl nitrite, temporary, almost transitory, relief from pain in twelve of twenty cases of duodenal ulcer and in six of ten cases of gastric ulcer, accompanied by a brief cessation of peristalsis and decrease in gastric tone. These observations apparently show that a sudden profound relaxation of the musculature may cause a brief respite from pain and suggest that frequently a combination of the mechanical and chemical forms of stimuli may be present—a summation effect.

The Effect of Antispasmodics.—The relief from spontaneous pain resulting from the injection of atropine sulphate has been attributed to an antispasmodic effect (Smith, Paul and Fowler [29]). While this possibility cannot be completely denied, our experiments suggest another explanation, for under certain conditions, atropine sulphate does not relieve the pain, and pain may be induced after atropinization by the introduction of acid into the stomach. The intravenous administration of atropine sulphate has two striking effects on the stomach: It stops motility temporarily and it inhibits secretion. The immediate result of the former is an abrupt cessation of gastric emptying. A rational hypothesis is that the alkaline duodenal content then bathes the surface of the ulcer, located in the duodenum, and stops the pain. We are not acquainted with any instances in which atropine sulphate has stopped the pain of gastric ulcer. Calcium chloride apparently acts in a similar manner, although it not only checks active peristalsis but also seems to induce reverse peristalsis, as is indicated by the marked nausea and occasional emesis noted. It is also quite likely that the marked peripheral vasodilation may have a transitory ameliorative effect on pain, regardless of its origin. The careful studies of Beams [38] on the effect of nitrites on ulcer pain have not been repeated by us. The brief but definite relief from pain noted by him in certain cases of gastric as well as duodenal ulcer cannot be explained on the basis of cessation of gastric emptying or reverse peristalsis. It is possible that the concomitant distracting subjective symptoms produced by the nitrites due to the peripheral vasodilation may have played an important rôle in the relief,

but, on the other hand, it is also quite possible that the sudden antispasmodic effect of the drug may have been sufficient to induce temporary relief. There were instances in the experiments of Beams in which the pain continued unrelieved by the nitrites just as it did in some of our experiments with calcium chloride.

Production of the Mechanism of Pain.—It has been seen that an irritable pain mechanism may be made to respond by the application of an adequate stimulus, mechanical or chemical. We have not yet considered the manner in which the stimulus affects the mechanism, how it produces pain. Meyer, Fetter and Strauss [41] ascribed the pain to ischemia and asphyxia due to depletion of the vascular bed in and about the ulcerous area, but Dragstedt and Palmer [49] noted that touching of the hyperemic serosa above the ulcer evoked pain without producing any vascular disturbance, and that the application of acid also produced pain without any discernible effect on the blood supply. The very painful circular spasm, on the other hand, was accompanied by a blanching of the contracted area. This is the normal effect of contraction in the bowel, and cannot be considered in itself as the cause of the pain. It may be noted further that Beams in his studies of the effect of nitrites on ulcer pain found no evidence of muscular spasm about the lesion, for the deformities in the stomach or intestine were not decreased by the nitrite, but were increased, the deformity being accentuated when the uninvolved portion of the stomach or intestine relaxed. Ivy,[48] according to Alvarez, suggested that the continuous type of distress might be due to congestion, edema and inflammatory reactions about the ulcer, all of which lower the threshold for stimuli, and that the intermittent type of pain might be due to changes in the tonicity of the muscle at the site of the ulcer, brought about by peristalsis or local spasm. Kinsella [47] considers the pain to be due to increased tension within the wall of the bowel, "congestion in indurated tissue aggravated by functional hyperemia." We are more inclined to regard increased tension in the tissues as a part of the inflammatory process and, as such, as partially responsible for the increased irritability and sensitivity. It therefore plays only an indirect rôle in the production of pain, although it is conceivable that when sufficiently acute, it alone may constitute an adequate stimulus.

The mechanical stimuli, usually due to peristaltic traction or localized muscular spasm, apparently act directly and mechanically on tissue whose sensitivity has been enhanced by the inflammatory process.[49] The action of chemical irritants is not so obvious. Three possibilities were postulated originally:[13] edema, localized muscular spasm and a direct effect on the nerve endings. It was stated at that time:

> The instantaneous production of severe pain which results at times in very sensitive ulcers from the injection of acid does not argue for the etiologic relationship of gross tissue edema to pain. Certain other characteristics of the pain make

it difficult to conceive of its being due to localized muscle spasm. It may come on gradually, being scarcely noticeable at first, and then, by almost imperceptible gradations increase in severity to intense pain. It disappears in a similar manner. As the sensitiveness of the pain-producing mechanism decreases, the latent period increases, the severity of the pain diminishes, and the pain threshold rises. This occurs in both benign and malignant ulcers. In benign ulcers, this decrease in the sensitiveness of the pain-producing mechanism seems to be related definitely to the healing process. Carcinomas can scarcely be said to heal, but the methods which desensitize a carcinoma are those which check peptic activity, prevent digestion of the slough and of poorly vitalized tissue, and thereby presumably protect the sensitive mechanism from the action of the chemical irritant. To me, these phenomena seem to suggest that the acid may act by direct irritation of exposed nerve endings rather than by the production of localized muscle spasm.

The evidence offered in the present paper seems to us to give further support to this view. The irritability or sensitivity of the tissue is so enhanced by the inflammatory process that the acid, acting on the tissue —probably directly on exposed nerve endings—becomes an adequate stimulus for the production of pain.

CONCLUSIONS

1. Ulcer pain arises at the site of the lesion.

2. It is not directly dependent on pylorospasm, gastric motility or intragastric pressure.

3. It depends on the presence of an adequate stimulus acting on an irritable pain-producing mechanism located in or adjacent to the lesion itself.

4. The enhanced irritability of the tissue in or about the lesion is dependent on the presence and continued action of acid gastric juice; conversely, desensitization may be produced by continued neutralization.

5. The *adequate* stimulus may be either (*a*) mechanical, due to peristaltic traction or local spasm; or (*b*) chemical, due to the acid reaction of the chyme.

6. The *usual* stimulus is the free hydrochloric acid of the gastric content.

7. The action of the stimulus, be it mechanical or chemical, is probably exerted directly on nerves rendered hyperirritable by inflammation resulting from the destructive effect of acid gastric juice.

PLASMOCHIN, PLASMOCHIN WITH QUININE SALTS AND ATABRINE IN MALARIA THERAPY

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The synthetic drug plasmochin, sometimes spelled plasmoquine, was developed in 1915. It is said to be (6 methoxy 8 α methyl δ diethylamino butyl) aminoquinoline. Thus, although it contains quinoline, it is not synthetic quinine.

At first this synthetic remedy was sold as plasmochin simplex. Later, quinine was added to it, and the combined product was called plasmochin compound. Finally, a larger percentage of quinine was added, and the mixture was sold as plasmochin with quinine salts. The latter has also been called quinoplasmoquine. At one time it was called beprochin.

Plasmochin is sold in the following forms:

1. Plasmochin simplex or plain: A salt of plasmochin, which is usually sold in bottles of twenty-five tablets, each tablet containing the equivalent of 0.02 Gm., or ⅓ grain, of plasmochin hydrochloride.

2. Plasmochin compound: Usually marketed in bottles of fifty tablets. Each tablet contains the equivalent of 0.01 Gm., or 1/6 grain, of plasmochin hydrochloride, combined with 0.125 Gm., or 2 grains, of quinine sulphate.

3. Plasmochin with quinine salts: Usually supplied in bottles of one hundred tablets. Each tablet contains the equivalent of 0.01 Gm., or 1/6 grain, of plasmochin hydrochloride, with 0.3 Gm., or 4½ grains, of quinine sulphate.

Recently a drug called atabrine has been marketed. This synthetic antimalarial substance is based on a heterocyclic system different from that of plasmochin. It is said by the manufacturers to be the dihydrochloride of 2 methoxy 6 chlor 9 (α methyl δ diethylamino butyl) aminoacridine, and at first it was called erion.

LABORATORY EXPERIMENTS

1. *Plasmochin and Plasmochin with Quinine Salts.*—Numerous laboratory studies with plasmochin have been reported since Roehl's

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original experiments,[1] especially those of Hegner and Manwell,[2] Manwell,[3] Wampler,[4] Fourneau and his associates et al.[5] and myself.[6a, b]

Several facts are apparent from these studies, in all of which canaries were used as experimental material. In the first place, plasmochin is definitely more effective than quinine against avian malarias. Roehl found plasmochin about sixty times more potent than quinine. Manwell stated that plasmochin was uniformly superior to quinine in the treatment of avian malaria. In a series of controlled experiments I [6c] found that in a canary which had received an experimental inoculation of Plasmodium cathemerium by needle, infection could invariably be prevented by intramuscular injections of plasmochin simplex in daily doses as small as 0.00016 Gm., provided the bird had received at least one dose of plasmochin subsequent to receiving the infective inoculum. This was a therapeutic rather than a prophylactic effect. Daily intramuscular injections of 0.0005 Gm. of quinine dihydrochloride did not protect the birds against infection from similar inoculations. The amounts of plasmochin and quinine used were maximal subtoxic doses for canaries which averaged 15 Gm. in weight.

The various avian malarias have been found to react differently to plasmochin. Manwell [3] noted that, although plasmochin was more effective than quinine in treating avian malaria, this superiority differed in degree according to the species of plasmodium.

Tests of the action of plasmochin on parasites of avian malaria in vitro were made by Manwell [3b] and by Nono and myself.[7] Manwell

1. Roehl, W.: Die Wirkung des Plasmochins auf die Vogelmalaria, Beihefte z. Arch. f. Schiffs- u. Tropen-Hyg. **30**:11, 1926; Naturwissenschaften **14**:1156, 1926.

2. Hegner, R., and Manwell, R. D.: The Effects of Plasmochin on Bird Malaria, Am. J. Trop. Med. **7**:279, 1927.

3. Manwell, R. D.: (*a*) Further Studies on the Effect of Quinine and Plasmochin on the Avian Malarias, Am. J. Trop. Med. **10**:379, 1930; (*b*) Quinine and Plasmochin Therapy in Plasmodium Rouxi Infections, with Further Notes on the Effects of These Drugs on the Other Avian Malarias, ibid. **12**:123, 1932.

4. Wampler, F. J.: A Preliminary Report on the Early Effects of Plasmochin on Plasmodium Cathemerium, Arch. f. Protistenk. **69**:1, 1930.

5. Fourneau, E.; Tréfouel, J., and Tréfouel, J. (Mme.); Stéfanopoulo, G., and Others: Contribution à la chimiothérapie du paludisme: Essais sur la malaria des canaris, Ann. Inst. Pasteur **44**:503, 1930.

6. Russell, P. F.: (*a*) Avian Malaria Studies: II. Prophylactic Plasmochin Versus Prophylactic Quinine in Inoculated Avian Malaria, Philippine J. Sc. **46**:347, 1931; (*b*) Plasmochin Simplex, a Prophylactic Drug in Avian Malaria, Am. J. Trop. Med. **11**:279, 1931; (*c*) Avian Malaria Studies: I. Prophylactic Plasmochin in Inoculated Avian Malaria, Philippine J. Sc. **46**:305, 1931.

7. Russell, P. F., and Nono, A. M.: Avian Malaria Studies: VII. Plasmochin as a Prophylactic Drug in Sporozoite Infections of Avian Malaria, Philippine J. Sc. **49**:595, 1932.

found that plasmochin had little effect on the infective qualities of Plasmodium elongatum unless it was allowed to act for six hours or more. On the other hand, Nono and I, working with Plasmodium capistrani, obtained results which indicated that plasmochin inactivated or devitalized asexual forms of the parasite (not sporozoites) when allowed to remain in contact with them in vitro for fifteen minutes.

The combination of plasmochin and quinine sold as plasmochin with quinine salts appears to be more effective against avian malaria than either quinine or plasmochin alone. For example, in a series of hitherto unpublished experiments I was able to sterilize the blood of each of six infected canaries by giving them daily intramuscular injections of plasmochin with quinine salts for a week. Each injection contained 0.00005 Gm. of plasmochin and 0.0015 Gm. of quinine hydrochloride. The parasite in this instance was Plasmodium capistrani, and injections were begun two weeks after a typical acute malarial attack. Sterilization of the blood was proved by injection into normal birds, with negative results, and by reinfection with the same strain of Plasmodium capistrani. In two other series of unpublished experiments I was unable to sterilize the blood of similarly infected canaries by similarly administered injections of quinine or of plasmochin simplex. The daily dose of quinine dihydrochloride was 0.0005 Gm.; that of plasmochin simplex was 0.0002 Gm. Plasmochin simplex at first appeared to produce the same results as plasmochin with quinine salts; in each case there was complete disappearance of parasites from the blood smears examined for thirty minutes. But in every instance a residual infection was present, as was shown by subsequent transference of the blood to uninfected birds and by the eventual reappearance of parasites in the blood smears of the birds which had received the drugs.

Manwell [3b] worked with Plasmodium praecox and Plasmodium cathemerium and administered plasmochin and quinine orally instead of intramuscularly. He reported that a combination of the drugs had only a slight if, indeed, any advantage over either drug administered alone. He also found wide differences in the susceptibility of individual birds to treatment. He interpreted this fact as indicating that the effect of plasmochin was exerted indirectly "through a stimulation of some sort to the natural defensive powers of the host, as well as directly upon the parasite." The fact that my results following intramuscular injection of the drug were more uniform than Manwell's [3] following oral administration may indicate that variation in response to treatment by mouth is due to differences in absorption of the drug rather than to any other cause.

Other laboratory experiments of interest are those of Epstein,[8] who tested the effect of plasmochin on the uterine muscle of cats and guinea-pigs in two ways: in situ in living animals, and when the muscle was excised and resting in a physiologic solution. On administering the drugs intravenously to cats, he found that definite uterine contractions were caused by quinine in doses of 0.004 Gm. per kilogram of body weight. This corresponds roughly to about 4 grains (about 0.26 Gm.) for an adult human being and is thus within the therapeutic dose of quinine. It required 0.001 Gm. of plasmochin per kilogram of body weight to cause similar contractions. This dose corresponds to about 1 grain (about 0.06 Gm.) for an adult human being and is about three times the usual therapeutic dose. Epstein concluded that plasmochin is safer than quinine during pregnancy, if given in a therapeutic dose, but that in larger doses it has a definite effect on the uterus.

Eichholtz,[9] experimenting with cats and rabbits, found that plasmochin in doses of more than 0.002 Gm. per kilogram of body weight, when administered intravenously, caused marked disturbance of the cardiac rhythm, but that this effect was of only short duration if the dose was reduced. When quinine was combined with plasmochin no arrhythmia occurred.

2. *Atabrine.*—Kikuth and his associates [10] found that atabrine administered to infected birds in their laboratories showed a therapeutic index of 1 : 30 as compared with a similar index for plasmochin and an index of only 1 : 4 for quinine. In birds in which infection with Plasmodium praecox was at its height atabrine reduced the number of parasites in the peripheral blood, but, like plasmochin, it did not cause their complete disappearance. In parallel experiments quinine had no effect on the number of parasites. These investigators found atabrine to be a schizontocide, differing from plasmochin, which is essentially a gametocide.

In rabbits and cats the relative minimum lethal doses of atabrine, given orally, as compared with those of quinine and plasmochin, expressed in grams per kilogram of body weight, are as follows:

	Quinine	Plasmochin	Atabrine
Rabbits	0.5	0.022	0.4 to 0.5
Cats	....	0.005 to 0.007	0.1 to 0.15

PRACTICAL THERAPEUTIC USEFULNESS

The ideal antimalarial drug would be inexpensive, easy and pleasant to take, nontoxic and capable of bringing about rapid alleviation of

8. Epstein, D.: A Comparison of the Action of Plasmoquine and Quinine on the Uterus, J. M. A. South Africa **5**:15, 1931.

9. Eichholtz, F.: Pharmacology of Plasmochin, Beihefte z. Arch. f. Schiffs- u. Tropen-Hyg. **31**:89, 1927.

10. Kikuth, W.; Sioli, F., and Peter, F. M.: (Atebrin) Zur Weiterentwicklung synthetisch dargestellter Malariamittel, Deutsche med. Wchnschr. **58**:530, 1932.

symptoms and quick destruction of all forms of all species of the plasmodium, including sporozoites, wherever they are hidden in the body. Needless to say, there is no drug or combination of chemicals which meets these requirements. Quinine, in the usual doses, is easy to take, is nontoxic and rapidly alleviates symptoms, but it is expensive, is not pleasant to take and does not quickly destroy the parasites. It has no effect at all on the sporozoites, so far as has been determined.

It will be apparent, I believe, from this review, that plasmochin and atabrine are valuable available adjuncts to quinine, but it will also be clear that the ideal antimalarial drug is still to be found. Plasmochin and atabrine are easy and pleasant to take, and they rapidly alleviate symptoms, but they are expensive, they must be administered with special care lest a toxic dose be given, and they do not destroy all forms of the parasite quickly. Plasmochin is more effective against the sexual forms of the plasmodium than quinine, but it does not seem to have any direct effect on sporozoites. It should be emphasized that plasmochin and atabrine do not replace quinine; rather, they supplement it.

1. *Plasmochin and Plasmochin with Quinine Salts.*—It is not possible to review, in this article, all the clinical experiments with plasmochin which have been published since the early reports of Sioli,[11] Mühlens [12] and others. For example, a number of useful studies were made by members of the medical department of the United Fruit Company [13] under the leadership of the late W. E. Deeks, who was quick to see the possibilities of plasmochin and plasmochin with quinine salts. So, too, Manson-Bahr,[14a, b] Sinton and his collaborators,[15] Hasselmann and

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11. Sioli, F.: Prüfung des Plasmochins bei der Impfmalaria der Paralytiker, Naturwissenschaften **14**:1160, 1926; Beihefte z. Arch. f. Schiffs- u. Tropen-Hyg. **30**:319, 1926.

12. Mühlens, P.: Die Behandlung der natürlichen menschlichen Malaria-Infektion mit Plasmochin, Beihefte z. Arch. f. Schiffs- u. Tropen-Hyg. **30**:25, 1926; Naturwissenschaften **14**:1162, 1926.

13. United Fruit Company, Medical Department, 15th to 20th Annual Rep., 1926-1931.

14. Manson-Bahr, P.: (*a*) The Action of Plasmochin on Malaria, Proc. Roy. Soc. Med. (Sect. Trop. Dis.) **20**:33, 1927; (*b*) Further Observations on the Effects of Plasmoquine and "Plasmoquine-Compound" on the Gametocytes of Benign Tertian and Subtertian Malaria, Lancet **1**:25, 1928; (*c*) The Therapeutic Effects of Plasmoquine in Pregnancy, ibid. **1**:882, 1932.

15. (*a*) Sinton, J. A.: Treatment of Malarial Fevers, Tr. Seventh Cong. (1927) Far Eastern A. Trop. Med. **2**:804, 1928; (*b*) Sinton, J. A., and Bird, W.: Studies in Malaria, with Special Reference to Treatment; Plasmoquine in the Treatment of Malaria, Indian J. M. Research **16**:159, 1928; (*c*) Sinton, J. A.; Smith, S., and Pottinger, D.: Studies in Malaria, with Special Reference to Treatment; Further Researches into Treatment of Chronic Benign Tertian Malaria with Plasmoquine and Quinine, Indian J. M. Research **17**:793, 1930.

Hasselmann-Kahlert,[16] Amies,[17] Kligler and Mer,[18] Manifold,[19] Schulemann[20] and many others have reported their clinical observations on the use of plasmochin alone or combined with quinine in the treatment of malaria.

At first, plasmochin alone was used, and, although there were some enthusiastic reports, it soon became evident that great care was required in administering this drug and that it was not always completely effective. Bass,[21] whose experience with quinine in malaria therapy is unsurpassed, in 1930 compiled from published reports the following list of toxic symptoms observed after the use of plasmochin: cyanosis, pallor, nausea, gastric pain, headache, dizziness, epistaxis, weakness and hemoglobinuria. He gave the following conclusions: "Plasmochin has a definite effect on clinical malaria, and both clinical and parasitic cures may be accomplished with it alone. Plasmochin has far less effect on malaria than has quinine, and its toxicity, which is associated with methemoglobinuria, makes its routine use questionable."

It is now generally agreed that the only justifiable use of plasmochin simplex is in instances in which quinine is contraindicated, as at times in blackwater fever, in pregnancy or in the presence of idiosyncrasy. For adults the usual dose is one tablet after breakfast and another after the evening meal on the first day, one tablet after each of the usual three meals on the second to the seventh day and the same dose of three tablets on three successive days of each week thereafter until the parasites and symptoms have disappeared. For children up to the age of 5 years the dose is usually half a tablet once or twice a day; for those from 6 to 10 years of age the dose is half a tablet three or four times a day. If cyanosis appears, the drug should be discontinued for a few days.

Observations of the medical staff of the United Fruit Company,[13] of Manson-Bahr[14a, b] and of others showed that plasmochin in combination with quinine had stronger curative action and less toxic effect

16. Hasselmann, C. M., and Hasselmann-Kahlert, M.: Plasmochin in Autochthonous Malaria in Tropical Regions, Philippine J. Sc. **37**:75, 1928; Deutsche med. Wchnschr. **55**:1635, 1929.

17. Amies, C. R.: Use of Plasmoquine in Subtertian Malaria, Bull. Inst. M. Research, Federated Malay States, no. 5, 1930, p. 1.

18. Kligler, I. J., and Mer, G.: Periodic Intermittent Treatment with Chinoplasmine as a Measure of Malaria Control in a Hyperendemic Area, Riv. di malariol. **10**:425, 1931; Studies on Malaria: VII. Relapse Rate After Quinine-Plasmoquine Treatment, Tr. Roy. Soc. Trop. Med. & Hyg. **25**:121, 1931.

19. Manifold, J. A.: Report on a Trial of Plasmoquine and Quinine in the Treatment of Benign Tertian Malaria, J. Roy. Army M. Corps **56**:321 and 410, 1931.

20. Schulemann, W.: Synthetic Anti-Malarial Preparations, Proc. Roy. Soc. Med. (Sect. Trop. Dis.) **25**:897, 1932.

21. Bass, C. C.: Treatment of Malaria, with Some Reference to Recently Promoted New Remedies, J. A. M. A. **95**:988 (Oct. 4) 1930.

than plasmochin alone. As a result plasmochin compound was marketed in the form of tablets which contained 0.01 Gm. of plasmochin combined with 0.125 Gm. of quinine sulphate. The usual dose of this compound is one tablet four times a day for adults, one tablet three times a day for children from 6 to 10 years old and one tablet twice a day for children under 6 years. It is best to give a 5 grain (0.3 Gm.) tablet of quinine with each tablet of plasmochin compound.

Plasmochin compound gave more satisfactory results than plasmochin alone, but the work of Sinton and his associates,[15] as well as that of others, showed that still better results could be obtained with more quinine than the compound contained. After extensive studies Sinton and his associates [15e] concluded, among other things, that plasmochin therapy requires constant supervision and control and that quinine and plasmochin in combination are better than either drug alone in producing permanent cures in chronic benign tertian malaria. They advised that not less than 1.25 Gm. of quinine be given daily, with not more than 0.04 Gm., "perhaps 0.03" Gm., of plasmochin. They recommended that no plasmochin be given to persons suffering from diseases of the kidneys, liver or circulatory system. They also believed that a prolonged course of small doses of plasmochin is better than a shorter course of larger and interrupted doses.

Manifold,[19] in India, after an adequate experiment, concluded that plasmochin and quinine combined could be given safely to all classes of British soldiers and to nearly all Indians. He observed few toxic results. He concluded that the treatment was "most efficacious in preventing relapses and a great advance on the ordinary quinine treatment." He used 0.04 Gm. of plasmochin and 1.25 Gm. of quinine daily in divided doses.

The present tendency is to give plasmochin with quinine salts in the following doses: for adults, one tablet three or four times daily, preferably after meals; for children between the ages of 1 and 5 years, half a tablet once or twice a day and for those between the ages of 6 and 10 years, half a tablet three or four times a day. As a rule, the fever will subside by the second or third day, and the parasites will disappear by the sixth or seventh day. Gametocytes are inactivated or destroyed almost at once. Treatment should be continued for two or three weeks.

Some observers, for example, Fischer and Weise [22] and Napier and Das Gupta,[23] recorded a provocative action of small doses of plasmochin.

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22. Fischer, O., and Weise, W.: Ueber Wirkungen und Nebenwirkungen des Plasmochins bei der Behandlung der menschlichen Malaria, Deutsche med. Wchnschr. **58**:1380 and 1421, 1927.

23. Napier, L. E., and Das Gupta, B. M.: Atebrin: A Synthetic Drug for the Treatment of Malaria, Indian M. Gaz. **67**:181, 1932.

The latter authors noticed this stimulating effect in an untreated patient who entered the hospital on the twelfth day of the month with a few trophozoites and crescents in the peripheral blood but with no fever. Daily examinations until the twenty-eighth revealed very few trophozoites on the twenty-second and only crescents in small numbers on the other days. On the twenty-fifth, twenty-sixth and twenty-seventh, two doses of 0.01 Gm. of plasmochin were given daily, and on the twenty-eighth there was a slight rise of temperature accompanying the reappearance of asexual forms of the parasite in blood smears. Similar results were observed by Napier, Butcher and Das Gupta.[24]

In human as in avian malaria, plasmodia react differently to quinine and to plasmochin, according to the stage of development. They also differ in their response according to their species; in fact, even different strains or races of the same species show marked differences in their susceptibility to these drugs. Schulemann,[20] for example, stated that quinine is most potent against benign tertian malaria, less so against quartan and least so against estivo-autumnal malaria in the acute attacks, i.e., against newly formed schizonts. Yet quinine is less effective in preventing relapses of benign tertian malaria than in preventing those of the estivo-autumnal type. It does not act effectively on the gametocytes of estivo-autumnal malaria, but plasmochin is of value against them. Plasmochin acts on both the schizonts and gametocytes of tertian and quartan malaria, although data on this point are not complete. But plasmochin is less effective against the schizonts of estivo-autumnal malaria. Unlike quinine, plasmochin is more potent in preventing relapses of benign tertian malaria than of the estivo-autumnal form. In fact, the usual 50 per cent rate of relapse in groups of laborers with benign tertian malaria after treatment with quinine is reduced to only 2 or 3 per cent when plasmochin is added to the quinine.

As was stated in the discussion of laboratory experiments, plasmochin is more suitable than quinine for the treatment of malaria in pregnancy, because it has less effect on the uterine muscles when given in the usual therapeutic doses. Nutter,[25] for example, specifically mentioned treating four pregnant women with plasmochin compound, without ill effects. Similar reports have been published by Mühlens and Fischer[26a] and by Manson-Bahr.[14c]

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24. Napier, L. E.; Butcher, D., and Das Gupta, C. R.: Field Experiments with Atebrin and Plasmochin, Indian M. Gaz. **67**:186, 1932.

25. Nutter, R. B.: Plasmochin, Annual Rep., M. Dept., United Fruit Company, 1926, vol. 15, p. 77.

26. Mühlens, P., and Fischer, O.: (*a*) Die Behandlung der natürlichen menschlichen Malaria mit Plasmochin, Beihefte z. Arch. f. Schiffs- u. Tropen-Hyg. **31**:7, 1927; (*b*) Ueber Malariabehandlung mit Atebrin, Arch. f. Schiffs- u. Tropen-Hyg. **36**:196, 1932.

The successful use of plasmochin in the treatment of blackwater fever has been reported by Mühlens and Fischer, Memmi and Schulemann,[27] Cooke and Willoughby [28] and others. But some investigators, for example, Brosius,[29] stated that plasmochin does not prevent the development of blackwater fever.

As to the effect of plasmochin on the spleen, Miller [30] and Manson-Bahr,[14a] among others, reported rapid reduction in the size of this organ following treatment with plasmochin; Miller stated that the decrease in size was much more rapid with plasmochin than with quinine.

2. *Atabrine.*—Information concerning atabrine is scanty, and the use of the drug must be considered as still in the experimental stage. Early publications seem to show that this drug has a destructive effect on the schizonts of all forms of malaria and on the gametocytes of tertian and quartan malaria but not on the crescents of estivo-autumnal infections. The dose provisionally recommended for adults is one tablet, i.e., 0.1 Gm., three times daily for a week. It is advisable, at least in cases of estivo-autumnal malaria to add to this treatment daily doses of 0.03 Gm. of plasmochin.

Among the published reports of the clinical use of atabrine should be mentioned those of Kikuth, Sioli and Peter,[10] Napier and Das Gupta,[23] Napier, Butcher and Das Gupta,[24] Das Gupta,[31] Mühlens and Fischer,[26b] James and his associates,[32] Thonnard-Neumann,[33] Drenowski,[34] Green [35] and Hoops.[36] Napier and Das Gupta, on the basis of

27. Memmi, G., and Schulemann, W.: Plasmochin, Synthetic Derivative of Quinoline, Beihefte z. Arch. f. Schiffs- u. Tropen-Hyg. **31**:59, 1927; Riv. di malariol. **6**:40, 1927.

28. Cooke, W. E., and Willoughby, H.: Note on Use of Intravenous Sodium Bicarbonate Solution in the Treatment of Blackwater Fever, Lancet **1**:334, 1929.

29. Brosius, O. T.: Plasmochin in Malaria, Rep. M. Dept., United Fruit Company, 1927, vol. 16, p. 26.

30. Miller, R. L.: Plasmochin in the Treatment of Malaria, J. M. A. Georgia **19**:363, 1930.

31. Das Gupta, B. M.: A Case of Blackwater Fever Treated with Atebrin, Indian M. Gaz. **67**:330, 1932.

32. James, S. P.; Nicol, W. D., and Shute, P. G.: A Study of Induced Malignant Tertian Malaria, Proc. Roy. Soc. Med. (Sect. Trop. Dis.) **25**:1153, 1932.

33. Thonnard-Neumann, E.: Ueber Behandlung der natürlichen Malaria mit Atebrin in Columbien, Arch. f. Schiffs- u. Tropen-Hyg. **36**:357, 1932.

34. Drenowski, A. K.: Therapeutische Versuche an Malariakranken mit Atebrin und Plasmochin, Arch. f. Schiffs- u. Tropen-Hyg. **36**:373, 1932.

35. Green, R.: Report on 50 Cases of Malaria Treated with Atebrin, a New Synthetic Drug, Lancet **1**:826, 1932.

36. Hoops, A. L.: The Treatment of Malaria with Atebrin in Estate Practice, Tr. Roy. Soc. Trop. Med. & Hyg. **26**:289, 1932.

eleven cases, concluded that atabrine in doses of 0.1 Gm. taken three times daily for four days controls fever in each of the three common forms of malaria, brings about a disappearance of asexual forms of the parasite from the peripheral blood and is neither toxic nor unpleasant to take. But they reported that atabrine did not destroy or prevent the formation of crescents of Plasmodium falciparum. They were not certain whether they had obtained complete cures or whether atabrine was more or less efficacious than quinine, but they believed that the results of the early experiments were encouraging. Napier, Butcher and Das Gupta, after treating a series of forty-eight patients under field conditions, concluded that atabrine in the doses used by Napier and Das Gupta exhibited "a considerable degree of efficacy," was safe and nontoxic and was suitable for use under field conditions. Hoops reported that atabrine administered under supervision is better than quinine for the treatment of malaria in estate practice. Treatment with the former drug is short, simple and less costly, and fewer relapses follow its use.

Das Gupta reported a case in which blackwater fever was successfully treated with atabrine. He used 0.1 Gm. twice a day for five days. In this case quinine had not been successful in controlling the disease; in fact, Das Gupta suggested that the hemoglobinuria was precipitated by quinine.

James and his associates [32] found atabrine useful in cases of infection with strains of Plasmodium falciparum, against which quinine had proved to be so ineffective that permanent cure by means of it could not be brought about. In other cases, in which different geographic strains of Plasmodium falciparum were involved, atabrine was found to be no better than quinine. In other words, as James and his associates pointed out, there are differing strains of Plasmodium falciparum. There are "geographic races" not morphologically different but having distinctive properties as regards clinical virulence, immunologic reactions and other biologic phenomena, including their reaction to drugs.

In this connection, it should be noted that it is not the ingested dose but the amount of the drug circulating in the blood stream and the length of time it remains there that should be considered in all comparisons of potency. The researches of Vedder and Masen,[37] St. John [38] and others in the analyses of quinine in the blood are important. No similar work has been reported with plasmochin and so little with quinine that most explanations of variations in response to malaria therapy must be considered as tentative.

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37. Vedder, E. B., and Masen, J. M.: The Determination of Quinine in the Blood as a Guide to the Treatment of Malaria, Am. J. Trop. Med. **11**:217, 1931.

38. St. John, J. H.: Quinine Analysis of the Blood with Reference to the Treatment of Malaria, Am. J. Trop. Med. **12**:101, 1932.

The research department of the Winthrop Chemical Company,[39] on the basis of reports concerning some seven hundred patients with malaria in different parts of the world who were treated with atabrine, has issued a statement summarizing the results. These seem to be consistent in showing that atabrine affects all forms of the three common species of plasmodia found in malaria, with the important exception of the gametocytes of the estivo-autumnal form. A further exception must be made in the case of all sporozoites. No information concerning the effect of atabrine on the latter is available. There is some evidence that atabrine actually tends to increase the number of crescents, but when plasmochin is added to the treatment, crescents are destroyed. It is not stated in the report whether quinine should be given with atabrine and plasmochin given in combination or with plain atabrine. The report stated further that splenomegaly is reduced by atabrine and that patients with blackwater fever have been successfully treated with this drug.

Mühlens[40] recently suggested the following method of treating malaria: 1. Estivo-Autumnal Malaria: For three days give one tablet each of atabrine (0.1 Gm.) and plasmochin simplex (0.01 Gm.) three times a day. Then for four days give only the tablet of atabrine (0.1 Gm.) three times a day. 2. Tertian and Quartan Malaria: Give simply one tablet of atabrine (0.1 Gm.) three times a day for from five to seven days. He stated that in his experience relapses did not occur after this treatment.

Among the ill effects of atabrine which are occasionally observed is a yellowish discoloration of the skin, due, it is said, to temporary deposition of the drug. This discoloration disappears within a period ranging from a few days to four weeks, without deleterious effect. Under treatment with atabrine and plasmochin given in combination there have been instances of abdominal pain similar to that which is sometimes observed following treatment with plasmochin.

SUMMARY

1. The origin and general nature of plasmochin, plasmochin compound, plasmochin with quinine salts and atabrine are briefly discussed, and a description is given of the forms in which each is available.

2. A number of laboratory experiments with these drugs, carried out by various observers, including myself, are discussed. From these it may be concluded that although the various avian malarias react differently to plasmochin and plasmochin with quinine salts, they are all

39. Winthrop Chemical Company, New York. Laboratory and clinical data concerning atabrine, prepared and mimeographed by the Department of Research Medicine, 1932.

40. Mühlens, P.: A lecture given on March 21, 1933, at the School of Hygiene and Public Health, University of the Philippines, Manila.

affected by it and by atabrine. Plasmochin combined with quinine is more effective than either drug used alone. Plasmochin in vitro is toxic to schizonts, more so to some species than to others. Plasmochin in doses exceeding the therapeutic limit causes uterine contractions in cats and guinea-pigs and cardiac arrhythmia in cats and rabbits. The effect on the uterus is not seen after therapeutic doses, and the disturbance of cardiac rhythm is not present when quinine is administered with the plasmochin.

3. The practical therapeutic usefulness of plasmochin, plasmochin compound, plasmochin with quinine salts and atabrine is considered, and reports of research workers in various parts of the world are given. It is concluded that plasmochin is best administered as plasmochin with quinine salts. Not more than 0.04 Gm. of plasmochin per day should be given to adults, and the administration of at least 1.25 Gm. of quinine in addition to or combined with the plasmochin is advisable. Larger doses of plasmochin produce toxic symptoms. Treatment should, as a rule, extend over two or three weeks.

4. It is concluded that plasmochin is not a substitute for quinine but an adjuvant to it. Quinine and plasmochin given in combination represent a distinct advance in malaria therapy. It is too early to draw definite conclusions concerning the merits of atabrine.

5. Not all cases of malaria are alike, and treatment should be given according to the characteristics of the plasmodium involved. Some patients react better to quinine; others, to plasmochin; others, perhaps, to atabrine. Plasmodia differ in their susceptibility to drugs according to stage of development, strain and species. Intelligent therapy will make use of these differences.

Book Reviews

The Technic of Local Anesthesia. By Arthur E. Hertzler, A.M., M.D., Ph.D., LL.D., Professor of Surgery, University of Kansas; Surgeon to the Halstead Hospital, Kansas. Fifth edition. Price, $5. Pp. 292, with 148 illustrations. St. Louis: C. V. Mosby Company, 1933.

In 1912 the Surgery Publishing Company of New York put out an unassuming small book called "Surgical Operations with Local Anesthesia," by Arthur E. Hertzler. The topic was something of a novelty, but the book was clearly written and well illustrated, winning at once a high degree of popularity. A second edition was necessary in 1916, which was considerably larger and better illustrated than the first. This was also enthusiastically received by students, surgeons and reviewers. In 1925 the C. V. Mosby Company published the third edition of the book under its present name. *The Journal of the American Medical Association* (**84**:1943 [June 20] 1925) devoted half a column to it, ending the review, after certain mild rebukes, in much the fashion of earlier reviewers: "These are minor criticisms, and are not meant as a criticism of the work as a whole, which is excellent and can be highly recommended." The fourth edition appeared in 1928, and now the fifth edition is off the press.

Any medical book which is only 21 years old and popular enough to have gone through five editions in so short a time is of necessity a first-class book. The original model was obviously built on serviceable lines, and the author has been sensible enough to retain its general plan in each ensuing edition. The latest publication, therefore, is much like its predecessors and is entirely praiseworthy. The chapter on spinal anesthesia has been rewritten, and a short chapter on intravenous anesthesia has been added to bring the subject up to date. The book as a whole continues to be informative, interesting, well illustrated and worth owning.

Strophanthin Therapy: Also Comments on the Quantitative Administration of Digitalis According to Pharmacologic Principles. By Prof. Dr. A. Fraenkel, in collaboration with Dr. R. Thauer. Pp. 144. Berlin: Julius Springer, 1933.

This monograph is amazingly complete in detail and is presented in a meticulously orderly and systematic manner. While the reader is at times burdened by detail, the work as a whole is very interesting.

The authors introduce the subject in a fascinating manner by relating the history of strophanthus. It was first introduced and grown in western Europe in 1800 by the French botanist, Descandolle. The interesting episode of Kirk's accidental discovery of its cardiac action while on Livingstone's expedition in Zambesia is told. The botanic facts regarding the plant are described in considerable detail, as are also the pharmacology and chemistry of strophanthin.

Every conceivable phase of the subject is considered, with emphasis on the indications, contraindications, methods of administration and results. After reading this monograph, one is led to wonder whether American physicians have accorded strophanthin proper recognition as a valuable cardiac drug.

Les grandes hémorragies gastro-duodénales. Étude Médico-Chirurgicale. By Louis Tixier and Charles Clavel. Price, 45 francs. Pp. 240. Paris: Masson & Cie, 1933.

This work is in accord with the French custom of treating a circumscribed aspect of medicine in monographic form. All types of gastroduodenal bleeding are discussed with the greatest thoroughness from every possible standpoint—clinical, anatomic, therapeutic and surgical. There are detailed case reports and

many illustrations. While a great amount of valuable material is assembled, one may make the criticism that very little is brought out which is not, or at least should be, common knowledge even among junior medical students, and a good many points are labored at undue length. The book contains a mine of material, however, and seems to give the last word on the subject. A good deal of discussion is devoted to indications for surgical intervention in cases of bleeding from the stomach. The authors point out that erosions of large arteries rarely heal spontaneously, and that the bleeding point should be ligated. They also admit the difficulty of making an exact diagnosis of this sort of accident and the further difficulty, often, of discovering the bleeding artery after the stomach has been opened. On the whole the reviewer would take a somewhat more conservative position than the authors; he believes that only occasionally is it advisable to operate during the course of gastric bleeding, as death, after all, rarely occurs purely from this cause.

Food, Nutrition and Health. By E. V. McCollum, Ph.D., Sc.D., and J. Ernestine Becker, M.A. Price, $1.50. Pp. 146. Published by the authors, Baltimore.

This book, now appearing in its third edition, is a most helpful guide in a day of general interest in foods and diets. The authors are head and associate, respectively, of the Department of Biochemistry of the School of Hygiene and Public Health of Johns Hopkins University. The book is, therefore, thoroughly authoritative. It contains a nontechnical account of the discoveries of nutrition and is of special service to both layman and physician as a corrective for the mass of misleading information being disseminated today by commercial interests and by the faddist.

The authors explain in simple language the essentials of a completely satisfactory diet, as revealed by the newer science of nutrition. The effects of deprivation of individual nutrients are explained; the kinds of malnutrition and their extent are described, and a system of diet is recommended which is sound not only from the physiologic but also from the economic standpoint.

The book is highly recommended for use in the medical school, in the office of the medical practitioner and in the household where interest has been aroused in matters of dieting and nutrition.

Verhandlungen der deutschen Gesellschaft für Kreislaufforschung. Edited by Prof. Dr. Bruno Kisch, Köln. Price, 15 marks. Pp. 276, with 97 illustrations and 35 charts. Dresden: Theodor Steinkopf, 1933.

This book, as the title indicates, consists of the papers presented at the sixth annual meeting of the Society. In addition to the president's address, there are twenty-eight papers together with the discussions. The papers cover all branches of the study of the circulation. Blood pressure, heart failure, the carotid sinus, electrocardiography, the vasomotor nerves and the parasympathetic and sympathetic systems are accorded a share of attention. The papers are profusely supplied with diagrams, charts and electrocardiograms.

The work is for the most part the result of experimentation on animals. There are a fair number of papers dealing with clinical observations of an experimental nature and a few purely clinical reports.

The work is well done but very highly specialized. For the research worker in this field or for the clinician who limits himself entirely to diseases of the circulation this book will prove extremely interesting and helpful. Apart from these groups its place is in the reference library, and it should be found in all good ones.

Chronic Indigestion. By Thomas C. Hunt. Price, $4.25. Pp. 341. Baltimore: William Wood & Company, 1933.

The material in this monograph is concisely and ably presented, and it will doubtless prove of value to students and practitioners alike. The author strives to give a practical outline of present-day views on chronic indigestion and related syndromes, based on personal experiences.

The first ten chapters are devoted to a discussion of the commoner organic and functional derangements of the gastro-intestinal tract. Accompanying each chapter are plates illustrating characteristic lesions as shown by roentgen examination. The routine laboratory procedures employed in this field are described, and a section is devoted to the taking of case histories, physical examination and special investigations.

A few prescriptions suitable for the treatment of "chronic indigestion" are included, the drugs employed being those in general use and of recognized value. A bibliography of about 168 references is included.

Surgery of the Stomach and Duodenum. By J. Shelton Horsley. Price, $7.50. Pp. 260. St. Louis: C. V. Mosby Company, 1933.

In this volume Dr. Horsley says about all there is to say on gastric surgery. The stage is set by brief chapters on embryology, anatomy and the physiology of the stomach, which are followed by detailed descriptions, well illustrated, of the various procedures. The reviewer is not competent to discuss the finer points of surgical technic. He does disagree, however, with some of the physiologic considerations which are supposed to furnish a rational basis for certain procedures. In his experience, for example, it is difficult to predict the results obtained by surgical intervention in cases of peptic ulcer. Sometimes the patient is helped; occasionally he is made worse. The effects are difficult to correlate with the mechanical changes which have been produced. The book is nicely gotten up, but the price is considered to be excessive.

Die Luft- und Fettembolie. By Siegfried Hoffheinz, M.D. Paper. Price, 29 marks. Pp. 259, with 50 illustrations. Stuttgart: Ferdinand Enke, 1933.

The author of this monograph gives an excellent account of air embolism and fat embolism. Both subjects are discussed systematically, in detail, and in much the same manner: historically, from the point of view of their pathology and pathologic physiology, and finally as clinical entities. A comprehensive bibliography completes the volume.

Such a book, dealing with two relatively uncommon surgical problems, is unlikely to acquire much popularity among general readers. As a reference book, however, it is to be recommended.

News and Notes

SURVEY OF INCIDENCE OF CRETINISM

A survey of the incidence of cretinism in the United States is proposed by Dr. Arnold Jackson (16 S. Henry Street, Madison, Wis.), who respectfully requests that physicians who have had such cases send to him the following information regarding them, together with photographs if possible: name and address of the patients, in order to obviate duplication; nativity; brief physical characteristics; brief clinical history; presence or absence of goiter; mental status, and the results of medication.

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